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Atopy Risk in Infants and Children in Relation to Early Exposure to Fish, Oily Fish, or Long-Chain Omega-3 Fatty Acids: A Systematic Review

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Abstract There are two main families of polyunsaturated fatty acids (PUFAs), the *n*−6 and the *n*−3 families. It has been suggested that there is a causal relationship between *n*−6 PUFA intake and allergic disease, and there are biologically plausible mechanisms, involving eicosanoid mediators of the *n*−6 PUFA arachidonic acid, that could explain this. Fish and fish oils are sources of long-chain *n*−3 PUFAs and these fatty acids act to oppose the actions of *n*−6 PUFAs. Thus, it is considered that *n*−3 PUFAs will protect against atopic sensitization and against the clinical manifestations of atopy. Evidence to examine this has been acquired from epidemiologic studies investigating associations between fish intake in pregnancy, lactation, infancy, and childhood, and atopic outcomes in infants and children and from intervention studies with fish oil supplements in pregnancy, lactation, infancy, and childhood, and atopic outcomes in infants and children. All five epidemiological studies investigating the effect of maternal fish intake during pregnancy on atopic or allergic outcomes in infants/children of those pregnancies concluded protective associations. One study investigating the effects of maternal fish intake during lactation did not observe any significant associations. The evidence from epidemiological studies investigating the effects of fish intake during infancy and childhood on atopic outcomes in those infants or children is inconsistent, although the majority of the studies (nine of 14) showed a protective effect of fish intake during infancy or childhood on atopic outcomes in those infants/children. Fish oil supplementation during pregnancy and lactation or during infancy or childhood results in a higher *n*−3 PUFA status in the infants or children. Fish oil provision to pregnant women is associated with immunologic changes in cord blood and such changes may persist. Studies performed to date indicate that provision of fish oil during pregnancy may reduce sensitization to common food allergens and reduce prevalence and severity of atopic dermatitis in the first year of life, with a possible persistence until adolescence with a reduction in eczema, hay fever, and asthma. Fish oil provision to infants or children may be associated with immunologic changes in the blood but it is not clear if these are of clinical significance and whether they persist. Fish oil supplementation in infancy may decrease the risk of developing some manifestations of allergic disease, but this benefit may not persist as other factors come into play. It is not clear whether fish oil can be used to treat children with asthma as the two studies conducted to date give divergent results. Further studies of increased long-chain *n*−3 PUFA provision in during pregnancy, lactation, and infancy are needed to more clearly identify the immunologic and clinical effects in infants and children and to identify protective and therapeutic effects and their persistence.

Keywords Atopy · Allergy · Asthma · Eczema · Immune function · Inflammation · Eicosanoid · Cytokine · Fatty acid · Fish oil · Pregnancy

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Abbreviations

AA	Arachidonic acid
ALA	α-Linolenic acid
CAPS	Childhood Asthma Prevention Study
COX	Cyclooxygenase
DHA	Docosahexaenoic acid
EPA	Eicosapentaenoic acid
FFQ	Food Frequency Questionnaire
IFN	Interferon
Ig	Immunoglobulin
IL	Interleukin
ISAAC	International Study of Asthma and Allergies in Childhood
LA	Linoleic acid
LOX	Lipoxygenase
LT	Leukotriene
PG	Prostaglandin
PUFA	Polyunsaturated fatty acid
RCT	Randomized controlled trial
SPT	Skin prick test
TNF	Tumor necrosis factor
TX	Thromboxane

Introduction

There are two main families of polyunsaturated fatty acids (PUFAs), the omega-6 (*n*−6) and omega-3 (*n*−3) families [1]. These are generally considered to act antagonistically to one another, such that relative imbalances may be associated with physiological dysfunction and increased risk of disease [2]. Intake of the *n*−6 PUFA linoleic acid (LA) increased over the latter part of the twentiath century and this has been said to be causally related to increased prevalence and incidence of atopic diseases in children [3, 4]. There is a plausible biological explanation for this relationship involving eicosanoid mediators produced from the long-chain *n*−6 PUFA arachidonic acid (AA), a derivative of LA [5, 6]. Because long-chain *n*−3 PUFAs act to counter the effect of *n*−6 PUFAs, a higher intake of these fatty acids should reduce the risk of atopic diseases [3, 4]. The richest food source of long-chain *n*−3 PUFAs is fish, especially oily fish, and they are also found in fish oil supplements. Therefore, it may be anticipated that higher consumption of fish or oily fish or use of fish oil supplements would be associated with lowered risk of atopy and its clinical manifestations. The aim of this article is to collate, describe, and interpret the current literature describing associations between early exposure to fish or to fish oil supplements and infant or childhood atopy or immune markers relevant to atopy; data from cohort, cross-sectional, case-control, and intervention studies involving pregnant or lactating women, infants, or children are considered. Prior to presenting this information, relevant background information on PUFAs and eicosanoids is presented.

Fatty acids: structure, nomenclature, sources, roles, and intakes

PUFAs contain two or more double bonds in their hydrocarbon (acyl) chain. A commonly used shorthand notation for describing and naming fatty acids relies upon identifying the number of carbon atoms in the chain, and the number of double bonds and their position. Thus, the 18-carbon fatty acid with two double bonds in its acyl chain and with the first double bond on carbon number 6 from the methyl terminal carbon is described as 18:2ω−6. The ω−*x* nomenclature is sometimes referred to as omega *x* (e.g. 18:2 omega 6) or *n*−*x* (e.g. 18:2*n*−6). In addition, fatty acids are often described by their common names. The main fatty acids of relevance to the current article are:

- Linoleic acid (LA; 18:2*n*−6)
- Arachidonic acid (AA; 20:4*n*−6)
- α-Linolenic acid (ALA; 18:3*n*−3)
- Eicosapentaenoic acid (EPA; 20:5*n*−3)
- Docosahexaenoic acid (DHA; 22:6*n*−3).

There are two principal families of PUFAs, the *n*−6 (or omega-6) and the *n*−3 (or omega-3) families. The simplest members of each family, LA and ALA, cannot be synthesized by mammals. LA is found in significant quantities in many vegetable oils, including corn, sunflower, and soybean oils, and in products made from such oils, such as margarines [1]. ALA is found in green plant tissues, in some common vegetable oils, including soybean and rapeseed oils, in some nuts, and in flaxseed (also known as linseed) and flaxseed oil. Between them, LA and ALA contribute over 95%, and perhaps as much as 98% of dietary PUFA intake in most Western diets [1], with LA intake being in excess of that of ALA. The intake of LA in Western countries increased greatly over the second half of the twentieth century, following the introduction and marketing of cooking oils and margarines [1]. ALA intake probably changed little over this time. Typical intakes of both essential fatty acids are in excess of requirements [1]. However, the changed pattern of consumption of LA has resulted in a marked increase in the ratio of *n*−6 to *n*−3 PUFAs in the diet. This ratio is currently between 5 and 20 in most Western populations [7, 8].

Although LA and ALA cannot be synthesized by humans, they can be metabolized to other fatty acids (Fig. 1). This is achieved by the insertion of additional

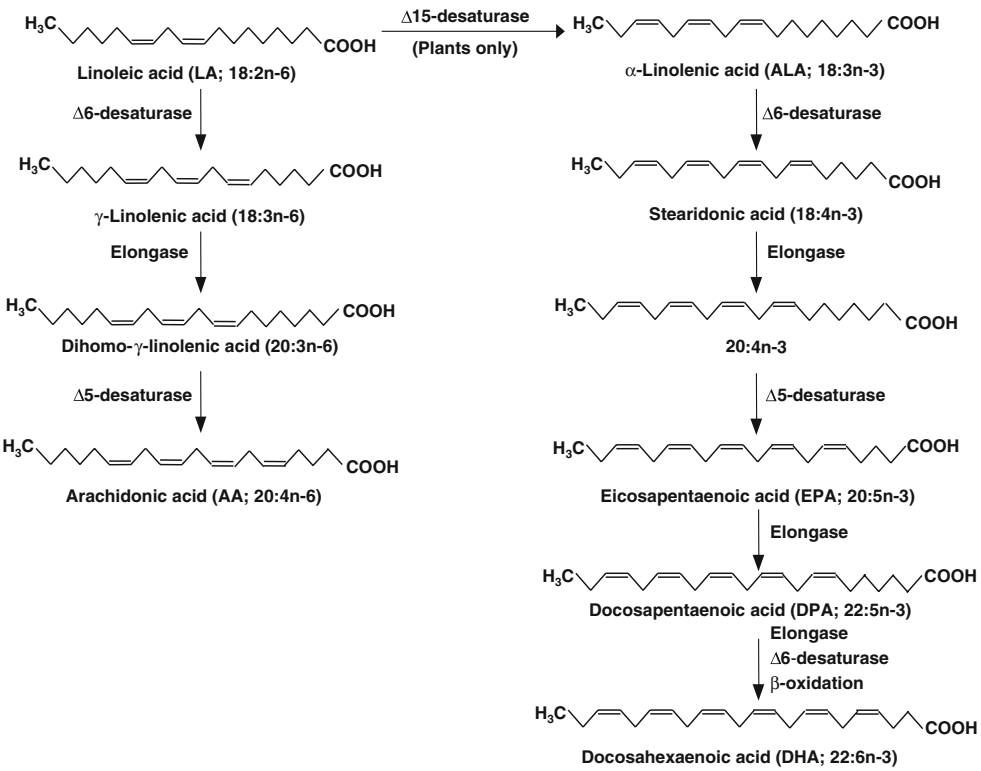

Fig. 1 The biosynthesis of *n*−6 and *n*−3 polyunsaturated fatty acids

double bonds into the acyl chain (i.e., unsaturation) and by elongation of the acyl chain. Thus, LA can be converted via γ-linolenic acid (18:3*n*−6) and di-homo-γ-linolenic acid (20:3*n*−6) to AA (Fig. 1). By an analogous set of reactions catalyzed by the same enzymes ALA can be converted to EPA. Both AA and EPA can be further metabolized, EPA giving rise to docosapentaenoic acid (22:5*n*−3; DPA) and DHA (Fig. 1). Dietary intakes of the longer chain, more unsaturated PUFAs are much lower than of LA and ALA [1, 8, 9]. AA is found in meat and offal and intakes are estimated at 50 to 500 mg/day. EPA, DPA, and DHA are found in fish, especially so-called "oily" fish (tuna, salmon, mackerel, herring, and sardine). One oily fish meal can provide between 1.5 and 3.5 g of these long-chain *n*−3 PUFAs [9]. The commercial products known as fish oils also contain these long-chain *n*−3 PUFAs, which typically will contribute about 30% of the fatty acids present. Thus, consumption of a typical 1-g fish oil capsule per day can provide about 300 mg of these fatty acids. In the absence of oily fish or fish oil consumption, intake of long-chain *n*−3 PUFAs is likely to be <100 mg/day, although foods fortified with these fatty acids are now available in many countries.

PUFAs, eicosanoids, inflammatory processes, and atopy

PUFAs play roles assuring the correct environment for membrane protein function, maintaining membrane fluidity and regulating cell signaling, gene expression and cellular function [1]. Through these actions PUFAs can influence the functioning of immune cells [10, 11] and so could impact on the development and manifestations of atopy [5, 6]. However, the key link between PUFAs and immunological processes related to atopy is that the eicosanoid family of mediators is derived from 20-carbon PUFAs [12, 13]. Because immune cells typically contain a high proportion of the *n*−6 PUFA AA and low proportions of other 20-carbon PUFAs [10, 11, 14], AA is usually the major substrate for eicosanoid synthesis. Eicosanoids, which include prostaglandins (PGs), thromboxanes (TXs), leukotrienes (LTs) and other oxidized derivatives, are generated from AA by the action of cyclooxygenase (COX) and lipoxygenase (LOX) enzymes (Fig. 2). These enzymes are expressed in inflammatory and epithelial cells and give rise to a mix of mediators depending upon the nature of cell types present and the nature, timing and duration of the stimulus [12, 13, 15, 16]. Eicosanoid mediators are involved in modulating the intensity and duration of inflammatory responses [see [15, 16] for reviews]. Through actions on dendritic cells, T cell differentiation and immunoglobulin (Ig) class switching in B cells, some eicosanoids (e.g. PGE_2) play a role in promoting sensitization to allergens. Through their actions on inflammatory cells, smooth muscles and epithelial cells, some eicosanoids are strongly implicated in different immunologic features and clinical manifestations of atopic disease (Table 1). Indeed, allergic inflammation in animal

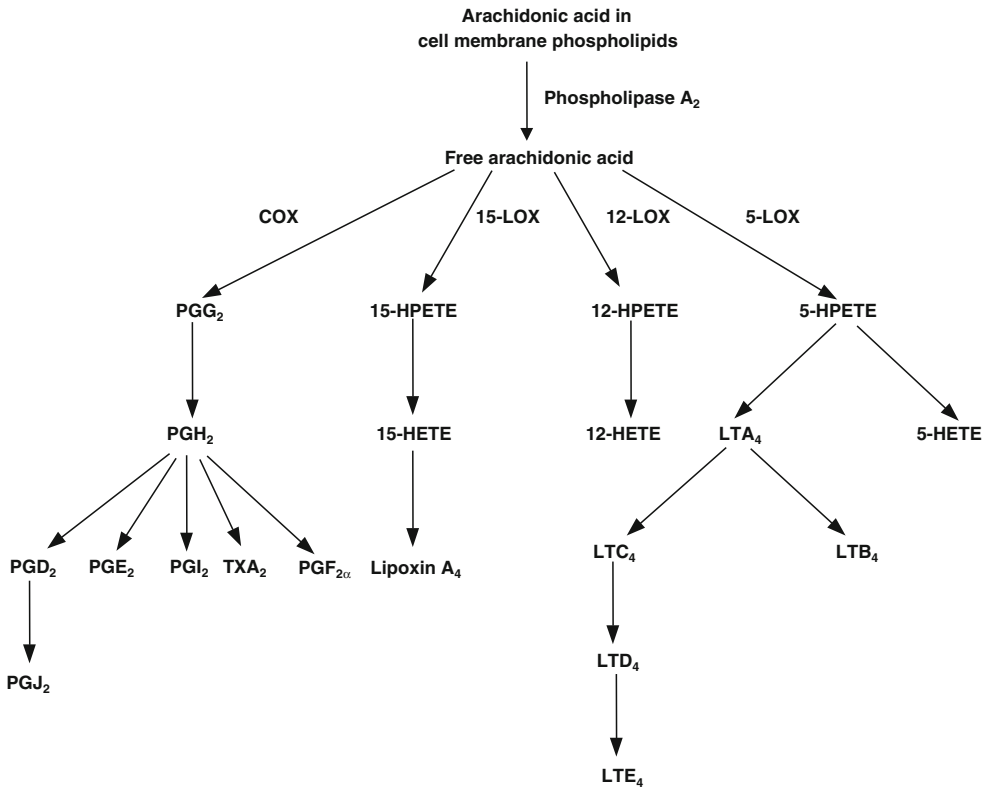

Fig. 2 Outline of the pathway of eicosanoid synthesis from arachidonic acid. *COX* cyclooxygenase, *HETE* hydroxyeicosatetraenoic acid, *HPETE* hydroperoxyeicosatetraenoic acid, *LOX* lipoxygenase, *LT* leukotriene, *PG* prostaglandin, *TX* thromboxane

models is associated with increased PG and LT production. However, inhibition of COX-1 or COX-2 or knockout of either COX results in augmented allergic inflammation with increased Th2 type cytokine production and increased airway reactivity (see [17, 18]). This suggests that the overall effect of PGs is to restrain allergic inflammation. However, individual PGs might enhance or inhibit allergic inflammation depending upon their specific action. One current view is that PGD_2, $PGF_{2\alpha}$, and TXA_2 increase allergic inflammation, whereas PGE_2 and PGI_2 inhibit it (see [17, 18]). PGD_2 is produced mainly by mast cells and activated macrophages. It is a potent bronchoconstrictor, promotes vascular permeability, and activates eosinophils and a Th2-type response. TXA_2 is a bronchoconstrictor and

Table 1 Selected effects of PGD_2, PGE_2, LTB_4 and cysteinyl leukotrienes

PGD_2	PGE_2	LTB_4	Cysteinyl LTs
Promotes bronchoconstriction	Increases vascular permeability	Increases vascular permeability	Vasodilation OR Vasoconstriction
Increases vascular permeability	Vasodilation	Enhances local blood flow	Promote smooth muscle contraction
Activates eosinophils	Inhibits Th1-type response	Chemotactic agent for leukocytes	Promote bronchoconstriction
Promotes Th2-type response	Promotes Th2-type response	Induces release of lysosomal enzymes	Increase vascular permeability
	Promotes IgE production by B cells	Induces release of reactive oxygen species	Promote mucus secretion
	Inhibits 5-lipoxygenase activity		
	Inhibits production of inflammatory cytokines (tumor necrosis factor-α, interleukin-1β)	Increases production of inflammatory cytokines (tumor necrosis factor-α, interleukin-1β)	
	Inhibits T cell proliferation	Promotes IgE production by B cells	
	Inhibits dendritic cell function		

stimulates acetylcholine release. PGE_2 is a vasodilator, increases vascular permeability, inhibits the production of Th1-type cytokines and primes naïve T cells to produce interleukin (IL)-4 and IL-5. PGE_2 also promotes Ig class switching in uncommitted B cells towards the production of IgE. Despite these effects of PGE_2, it is now considered that this eicosanoid is protective towards airway inflammation [17, 18]. It is possible that PGE_2 promotes sensitization via its effects on T cell phenotype and B cells, but is protective against the subsequent manifestations of inflammation upon re-exposure to allergen. PGI_2 appears to suppress Th2 lymphocyte activity and eosinophil recruitment. LTB_4 is chemotactic for leukocytes, increases vascular permeability, induces the release of lysosomal enzymes and reactive oxygen species by neutrophils and of inflammatory cytokines (e.g., tumor necrosis factor (TNF)-α) by macrophages, and promotes IgE production by B cells. The cysteinyl LTs (LTC_4, D_4, and E_4) may be either vasoconstrictors or vasodilators depending upon the situation and the location of their synthesis. They cause smooth muscle contraction and bronchoconstriction, increase vascular permeability and eosinophil recruitment, and promote mucus secretion. PGE_2 inhibits 5-LOX activity, down-regulating LT production [19]. Furthermore, PGE_2 induces 15-LOX leading to production of lipoxin A_4 which is anti-inflammatory [20, 21]. These effects highlight the antagonist nature of eicosanoids and may underlie, at least in part, the protective effect of PGE_2 in allergic inflammation.

Animal feeding studies have shown a strong positive relationship between the amount of AA in inflammatory cells and the ability of those cells to produce eicosanoids such as PGE_2 [22]. A recent human study also reported a strong positive correlation between the amount of AA in mononuclear cells and their ability to produce PGE_2 when stimulated by lipopolysaccharide [23].

Increased consumption of long-chain *n*−3 PUFAs such as EPA and DHA (usually given as fish oil) results in increased proportions of those fatty acids in inflammatory cell phospholipids (see [10, 11, 14, 23]). The incorporation of EPA and DHA into human inflammatory cells occurs in a dose-related fashion [23, 24] and is partly at the expense of AA. Since there is less substrate available for synthesis of eicosanoids from AA, fish oil supplementation of the human diet has been shown to result in decreased production of a range of AA-derived eicosanoids by inflammatory cells (see [14] for references). EPA is also able to act as a substrate for COX and LOX enzymes, giving rise to eicosanoids with a slightly different structure to those formed from AA (e.g., 5-series LTs; see [14]). The functional significance of this is that the mediators formed from EPA are believed to be less potent than those formed from AA. For example, LTB_5 is ten to 100-fold less potent as a neutrophil chemotactic agent than LTB_4 (see [14]).

In addition to long-chain *n*−3 PUFAs modulating the generation of eicosanoids from AA and to EPA acting as substrate for the generation of alternative eicosanoids, recent studies have identified a novel group of mediators, termed E and D-series resolvins, formed from EPA and DHA, respectively, that appear to exert anti-inflammatory and inflammation resolving actions (see [25] for a review). In recent studies in ovalbumin-sensitized Balb/C mice administration of resolvin E1 was found to decrease airway eosinophil and lymphocyte recruitment, production of the Th2 cytokine IL-13, circulating ovalbumin-specific IgE, and airway hyperresponsiveness to inhaled methacholine [26] and to promote the resolution of inflammatory airway responses by directly suppressing the production of IL-23 and IL-6 in the lung [27].

The above considerations have led to the idea that a high exposure to *n*−6 PUFAs (and/or low exposure to *n*−3 PUFAs) will promote atopy (both sensitization and manifestations) and that high exposure to *n*−3 PUFAs will be protective [3–6].

Epidemiological studies relating early fish exposure to atopic outcomes in infancy or childhood

The aim of this section is to describe and interpret studies relating maternal fish intake during pregnancy or lactation to atopic outcomes in the offspring of those mothers and relating fish intake during infancy or childhood to atopic outcomes in those infants or children. Studies were identified through Ovid Medline (1950–2009) and Embase (1980–2009) databases performing and combining searches using appropriate keywords.

Studies investigating the effect of maternal fish intake during perinatal life on atopic outcomes in infants or children

Table 2 summarizes all identified studies that investigate the association between maternal fish intake in perinatal life (five studies of fish intake during pregnancy and one study of fish intake during lactation) and atopic outcomes in the offspring of those mothers.

Out of the five studies which examined the effect of maternal fish intake during pregnancy three studies were prospective cohort [28–30], one study was case–control [31], and one study was retrospective cohort [32]. The age range of children taking part in these studies was between 2 and 16 years. Children who took part in the three prospective cohort studies were followed-up for 6, 2, and 5 years [28–30] for each study, respectively. Table 2

Table 2 Summary of studies of maternal fish intake during pregnancy or lactation and atopic or allergic outcomes in infants and children of those mothers

Reference	Study population and design	Exposure measures and exposure assessment	Outcome measures and confounding factors	Findings
[31]	279 asthmatic and 412 non-asthmatic children (4th, 7th, 10th grade) and their mothers/ guardians Nested case-control study in the Children's Health Study Public schools in southern California, USA	Maternal fish consumption during pregnancy - retrospective assessment (1999–2001): Oily fish (> 2% fat) Non-oily fish (≤2% fat) Fish fingers ('fish sticks') Canned fish Frequency questionnaire - telephone interviews: Never Rarely At least 1/month	Parental report of physician-diagnosed by age 5 years: any asthma, early transient asthma, early persistent asthma, late-onset asthma (1993–1995) Confounding factors: maternal asthma, race/ethnicity, maternal age, maternal education, gestational age, number of siblings, exclusive breast feeding for four months, other fish categories	Asthmatic mothers: at least monthly oily fish consumption during pregnancy vs. never associated with decreased risk of any asthma in children (OR 0.20; 95% CI 0.06–0.65; *p*-trend 0.006). Asthmatic and non-asthmatic mothers together: maternal oily fish consumption at least monthly associated with decreased risk of early persistent asthma in children (OR 0.45; 95% CI 0.23–0.91; *p*-trend 0.04) Fish fingers consumption associated with increased risk of any asthma (OR 2.04; 95% CI 1.18–3.51; *p*-trend 0.01) Children of non-asthmatic mothers did not benefit from maternal oily fish consumption during pregnancy No associations were found for non-oily of canned fish
[32]	295 allergic and 693 non-allergic mothers and their children (median age 5 years, range 17 years) Retrospective cohort General Hospitals in Rome, Italy	Maternal intake of fish, butter, margarine during pregnancy Retrospectively assessed by parental report via standardized questionnaire: 1 time/month or less 1 time/week 2–3 times/week or more	Atopy in children: SPT to inhalant and food allergens (at hospital) Confounding factors: age, gender, oculorhinitis, eczema, age of gestation, maternal smoking, paternal atopy, maternal occupation, butter and margarine intake	Non-allergic mother group: A reduction in risk of food sensitisations in offspring of mothers with fish intake during pregnancy '1 time/week' (OR 0.22; 95% CI 0.08–0.55; *p*-trend 0.002) and '2–3 times/week or more'(OR 0.23; 95% CI: 0.08–0.69; *p*-trend 0.002) compared to 1 time/month or less Intake of fish '1 time/week' and '2–3 times/week or more' associated with decreased milk sensitisation (OR 0.15; 95% CI 0.04–0.59 and OR 0.05; 95% CI 0.00–0.54 respectively) and egg sensitisation (OR 0.26; 95% CI 0.09–0.76 and OR 0.33; 95% CI 0.10–1.07 respectively) No associations with inhalant sensitisation Allergic mother group: no associations between maternal intake of fish during pregnancy and children food or inhalant sensitization Whole study population (adjusted also for maternal atopy): Increased consumption of fish associated with decreased prevalence of positive SPT for foods (*p*-trend 0.008) Fish intake '1 time/week' vs ≤1 time/month associated with decreased risk of food sensitization (OR 0.34; 95% CI 0.15–0.75; -*p*=0.007)
[29]	462 pregnant women and their offspring (follow up at age 1 and 6 years)	Maternal dietary intake during pregnancy including fish: Total fish Oily fish Non-oily fish	Parental report: doctor-diagnosed eczema (at age 1 year), atopic wheeze and persistent wheeze (at age 6 year) SPT (at age 6 years)	An increase in maternal fish intake during pregnancy from once per week to 2.5 times per week associated with lower risk of eczema at age 1 year (OR 0.73; 95% CI 0.55–0.98; *p*=0.036), positive SPT for HDM at 6 years (OR 0.68; 95% CI 0.46–1.01; *p*=

Table 2 (continued)

Reference	Study population and design	Exposure measures and exposure assessment	Outcome measures and confounding factors	Findings
	Prospective cohort Antenatal Clinics in Manorca, Spain	Interviewer administered FFQ; 3 months after delivery: Weekly intake	IgE (at age 4 years) Confounding factors: maternal asthma, type of fish, smoking during pregnancy, maternal atopy, gender, maternal social class, gestational age	0.058), and atopic wheeze at age 6 years (OR 0.55; 95% CI 0.31–0.96; p=0.034) Weekly maternal fish intake during pregnancy was associated with eczema at 1 year (p=0.050), positive SPT for HDM at 6 years (p=0.048), atopic wheeze at 6 years (p=0.028) Stratification by breastfeeding: an increase in fish intake during pregnancy from 1 time/week to 2.5 times/week associated with decreased risk of persistent wheeze at 6 years by 90% (OR 0.10; 95% CI 0.02–0.69; p<0.05) among the non-breastfed infants
[28]	2,641 mothers and their infants followed up to age 2 years Prospective cohort in the Influences of Lifestyle Factors on the Immune System and the Development of Allergies in Childhood Study (LISA) Newborns from 4 German cities	Maternal diet during the last 4 weeks of pregnancy including fish Semi-quantitative FFQ administered shortly after delivery: High (1–2 times/week) Low (<1 time/week)	Parental report of lifetime doctor-diagnosed eczema at age 2 years Allergic sensitization (IgE) Confounding factors: study area, sex, maternal age at delivery, smoking during 2nd or 3rd trimester of pregnancy, parental education, exclusive breastfeeding for≥4 months, family history of atopy, season of birth, all dietary variables from FFQ	High maternal fish intake vs. low associated with decreased doctor-diagnosed eczema risk in children at 2 years (OR 0.75; 95% CI 0.57–0.98; p<0.05)
[30]	1212 pregnant women and their children followed up to age 5 years Prospective cohort Aberdeen Maternity Hospital, Scotland	Maternal diet during pregnancy including fish; reflecting intake 2–3 months prior to 32 weeks gestation: Total fish Oily fish Semi-quantitative FFQ: Version 5.4 of the Scottish Collaborative Group FFQ; sent by post and self-administered at 32 weeks gestation: Never <1/week 1/week ≥1/week	Parental report of asthma, atopic eczema, wheezing, hay-fever in children at 5 years (ISAAC core questions) Spirometry and SPT (only on small number of children) Confounding factors: maternal age of leaving full-time education, paternal social class, maternal age, maternal smoking during pregnancy, smoking in the home during childhood, energy intake, maternal asthma, maternal atopy, birth weight, presence of older siblings, child's gender, breastfeeding	Maternal total fish intake≥1/week vs. never associated with decreased risk of doctor-diagnosed eczema (OR 0.57; 95% CI 0.35–0.92; p-trend 0.008), current treated eczema (OR 0.58; 95% CI 0.32–1.06; p-trend 0.028), and ever having eczema (OR 0.68; 95% CI 0.43–1.10; p-trend 0.05) Maternal oily fish intake≥1/week vs. never associated with decreased risk of doctor-diagnosed hay-fever (OR 0.28; 95% CI 0.06–1.19; p-trend 0.043)
[33]	34 atopic mothers and their infants followed up to age 1 year	Breast milk fatty acids; samples taken 1 month postpartum when infants were exclusively or predominantly breastfed Maternal atopic disease (asthma, allergic rhinitis, atopic dermatitis) assessed with questionnaire and SPT; 35-36 weeks of gestation	Clinical examination at ages 1, 3, 6, 12 months and SPT at 12 months Atopic dermatitis during the 1st year of life (Hanifin criteria)	Maternal frequency of fish consumption during pregnancy was not related to breast milk EPA content. The ratio SFA/PUFA was higher in breast milk consumed by infants developing atopic dermatitis compared to those remaining healthy (4.3 vs 3.1; p=0.05)

Table 2 (continued)

Reference	Study population and design	Exposure measures and exposure assessment	Outcome measures and confounding factors	Findings
	Finland	Maternal dietary intake (4-consequative-day food records) and questionnaire on maternal dietary habits including fish consumption frequency; 1 month postpartum reflecting intake during lactation <1 time/week 1 time/week >1 time/week		Total *n*−3 PUFA (% of total fatty acids) was lower in the breast milk of mothers whose infants developed atopic dermatitis than of those whose infants remained healthy (1.61% vs 2.17%; $p=0.05$) EPA (% of total fatty acids) was lower in breast milk consumed by infants who developed atopic dermatitis during the 1st yr of life compared to those who did not (0.10 vs 0.15; $p=0.02$)

OR odds ratio, *CI* confidence interval, *PUFA* polyunsaturated fatty acids, *SFA* saturated fatty acids, *HDM* house dust mite, *FFQ* food frequency questionnaire, *ISAAC* International Study of Asthma and Allergies in Childhood, *SPT* skin prick testing, *DHA* docosahexaenoic acid, *EPA* eicosapentaenoic acid, *Ig* immunoglobulin, *vs*. versus

presents only statistically significant effects of maternal fish intake in relation to atopic outcomes in the infants or children. Other results reported by these studies that were either not significant or not related to fish intake are not included here. Regarding the quality and the method of assessing fish intake during pregnancy, three of the five studies used a food frequency questionnaire (FFQ) [29, 31, 32] and two used a semi-quantitative FFQ [28, 30]. FFQs varied in frequency categories and also in time point of administration (during pregnancy [30], shortly after birth [28, 29] or retrospectively some time after birth [31, 32]) and way of administration (self-administered [30] or interviewer-administered [28, 29, 31]). All of the studies adjusted for most recognized confounding factors. There was great heterogeneity among studies with regard to the outcome measures and their assessment. Salam et al. [31] focused on asthma, Calvani et al. [32] focused on allergic sensitizations, while Sausenthaler et al. [28], Romieu et al. [29], Willers et al. [30] included various outcome measures such as eczema, atopic wheeze, allergic sensitization, or hay fever. Each of the studies assessing clinical outcomes used a parental questionnaire which most of the time asked for doctor diagnosis and gave clear definitions of each outcome. Although doctor-diagnosed atopic diseases may be more valid, limited access to health care may result in under-diagnosis of atopic disease, especially when these are mild or at early stages [31].

There is consistency between the findings of these five studies since each of them identified beneficial associations between maternal fish intake during pregnancy and atopic or allergic outcomes in children (Table 2). In the study of Salam et al. [31] the association between maternal oily fish intake and children's risk of developing asthma was greater in children whose mothers had asthma compared to children of non-asthmatic mothers (p for interaction= 0.02). In contrast, Calvani et al. [32] observed stronger and more significant beneficial effects of increased oily fish intake during pregnancy for children of non-allergic mothers compared to those of allergic mothers for food sensitizations (p for trend=0.002) but not for inhalant sensitizations. It is not clear why these findings are different. In the prospective cohort study conducted by Romieu et al. [29], although a beneficial association was observed initially for the whole sample, after stratifying by breast-feeding, increased fish consumption during pregnancy decreased the risk of persistent wheeze at 6 years of age among the non-breastfed infants whereas no protective effect was observed among the breastfed infants. The large cohort studies conducted by Sausenthaler et al. [28] and Willers et al. [30] concluded similar associations: high (≥1 time/week) vs. low maternal fish intake during pregnancy was associated with decreased doctor-diagnosed eczema. However, the decrease in the study of Willers et al. [30] was greater than that in the study of Sausenthaler et al. [28] (43% vs. 25%, respectively). This might be related to the fact that the study of Willers et al. [30] followed-up children for a longer period, allowing for manifestations of atopic disease to be revealed at the stage of clinical assessment. Willers et al. [30] also showed that there was 72% less doctor-diagnosed hay fever in children born to mothers with higher oily fish intake (but not total fish intake) during pregnancy. Across these five studies, the extent of the protective effect of maternal fish intake was highly variable. Fish intake resulted in a decrease in infant or childhood atopy which ranged between 25% and 95%. However, most decreases in atopic risk ranged between 40% and 80%.

The last study listed in Table 2 conducted by Hoppu et al. [33] assessed maternal dietary intake 1 month after birth (during lactation) and atopic dermatitis development in the infant at four timepoints. The primary objective of the study was to examine the effect of breast milk fatty acid

composition on atopic dermatitis during the first year of life. Although a higher percentage of EPA in breast milk was related to lower risk of atopic dermatitis, fish consumption frequency during lactation was not associated with breast milk EPA content. This may be explained by the fact that breast milk fatty acid composition is determined more by fatty acids accumulated in maternal adipose tissue during pregnancy rather than dietary intake of fatty acids during lactation [34, 35]. The authors stated that maternal fish intake during pregnancy would have been more appropriate to investigate in relation to breast milk composition [33].

Summary and discussion of the findings of these studies

All five epidemiological studies investigating the effect of maternal fish intake during pregnancy on atopic or allergic outcomes in infants/children of those pregnancies concluded protective associations. The protective effect varied widely between 25% and 95% and this might be attributed to differences in study design, i.e., confounding factor adjustments, statistical analysis, definition of atopic outcome in infants/children and their mothers, method of atopy evaluation, method of collecting dietary information, oily and/or total fish definition as well as categories of consumption frequencies used for comparisons. The one study investigating the effects of maternal fish intake during lactation did not observe any significant associations.

Studies investigating the effects of fish intake during infancy or childhood on atopic outcomes in those infants or children

Table 3 summarizes all identified studies that investigate the association between fish intake during infancy or childhood and atopic or allergic outcomes in those infants or children; 14 studies were identified. Nine studies observed a beneficial effect of fish intake during infancy/childhood and atopic outcomes in those infants/children [36–44]. Two of the studies observed a negative effect of fish intake on childhood atopy [45, 46], and three studies observed no associations [47–49].

Of the studies that found a beneficial association between fish intake during infancy/childhood and atopic outcomes, three were prospective cohort [38, 41, 49], two were case–control [36, 37], and four were cross-sectional [39, 40, 42, 43]. The age range of children taking part in these studies was between 1 and 18 years (at the time point that outcomes were measured). Because of the wide age range of the study population, differences in the extent of the beneficial effect can be expected. Some of the studies measured exposure and outcome at a much older age [36, 37, 39, 40] than others [38, 41, 42, 49]. Two of the prospective cohort studies followed-up infants to age 4 years [38, 41], whereas Alm et al. [49] followed-up infants to age 1 year. Atopic outcome definitions and assessment methods differed between studies. Three of the studies performed skin prick testing (SPT) [36, 39, 42] and one study determined specific IgE to identify sensitization [41]. In the study of Alm et al. [49] no clinical test or biochemical measurement of allergy was conducted. Clinical outcomes in all of the studies were assessed with parental questionnaires. However, parents were not always asked for doctor diagnosis. The different studies controlled for different confounding factors.

The reduction in atopy/allergy risk due to fish intake among these nine studies ranged between 22% and 80% (Table 3). However, the risk reduction in most cases was between 50% and 60%, providing consistent evidence for the protective effects of fish consumption during infancy/childhood on atopy/allergy. The study of Antova et al. [43] showed that low fish intake, compared with higher intake, increased the risk of respiratory symptoms by 21% (current wheeze). However, studies were inconsistent as far as exposure assessment is concerned. All three prospective cohort studies [38, 41, 49] determined the time point of fish introduction during the first year of life using a parental questionnaire. In addition, Kull et al. [41] collected information on fish consumption frequencies. The cross-sectional studies of Kim et al. [40] and Antova et al. [43] used a parental FFQ, that of Chatzi et al. [42] used a semi-quantitative FFQ and the other cross-sectional study used parental report of fish consumption without frequencies [39]. The retrospective case–control study of Dunder et al. [37] used a 48-h recall of intake and the case–control study of Hodge et al. [36] used a parental FFQ (although consumption frequency categories were not used in their analysis). The ideal method of collecting information on fish consumption would be a FFQ with various food categories/items reflecting intake during the past 12 months, including time of introduction of fish into diet and different types of fish consumed (oily, non-oily). Oily fish consumption was recorded in only some of the studies [36, 42, 49]. The rest of the studies recorded only total fish intake without specifying the types of fish. In the study of Hodge et al. [36], fresh oily fish consumption had a greater beneficial effect on current asthma than total fish consumption (74% versus 48% reduction, respectively). The 'Infants of Western Sweden' study of Alm et al. [49] collected information on the fish usually consumed and this was categorized into two different types of fish (lean and oily). The vast majority of the infants consumed lean fish, and at the univariate analysis it was shown that eating lean fish reduced eczema risk by 19% at 1 year of age, but the effect was lost at the multivariate analysis [49]. However, Chatzi

Table 3 Summary of studies of fish intake during infancy/childhood and atopic or allergic outcomes in those infants/children

Reference	Study population and design	Exposure measures and exposure assessment	Outcome measures and confounding factors	Findings
[36]	468 children aged 8–11 years Case–control Sydney, Australia	Dietary intake of children including fish (reflecting intake over the last year): Total fish (all categories) Fish fingers Canned fish Total fresh fish Fresh oily fish (>2% fat) Fresh non-oily fish (≤2% fat) FFQ completed by parents: Yes No	Assessed 6 months before dietary information was collected: AHR (by exercise), SPT, recent wheeze (parental questionnaire) Current asthma: presence of both recent wheeze and AHR Confounding factors: sex, ethnicity, country of birth, atopy, respiratory infection in the first 2 years of life, parental smoking or asthma history	Unadjusted analysis: Total fresh fish (OR 0.50; 95% CI 0.27–0.92; $p<0.05$) and oily fresh fish (OR 0.29; 95% CI 0.13–0.67; $p<0.01$) associated with reduced risk of current asthma Adjusted Analysis: Oily fresh fish associated with reduced risk of current asthma (OR 0.26; 95% CI 0.09-0.72; $p<0.01$)
[46]	114 asthmatic and 202 non-asthmatic children; aged 12 years Case–control Saudi Arabia (rural and urban areas)	Dietary intake including fish at age 12 years: Maternal completion of semi-quantitative FFQ; Questionnaire on food types and dietary habits: Often Sometimes Rarely Never	Asthma ever, wheeze in the last 12 months (ISAAC questions answered by the children), SPT Cases: both asthma and wheeze Confounding factors: social class, place of residence, nationality, sex, maternal education, family history of asthma or allergy, positive SPT	Univariate analysis: The frequency of eating fish was not significantly related to ever having asthma or wheezing in the last 12 months
[37]	1. Retrospective case-control nested in the 9-year follow-up (1980–1989): 60 atopic and 1293 non-atopic children aged 3, 6, 9, 12, 15, 18 years 2. Case-control: 231 atopic and 231 non-atopic children (1980); mean age 10.3 years 154 atopic and 154 non-atopic children (1986) (pairs matched for age, sex and place of residence) Finland (rural and urban areas)	Dietary intake including fish intake (standardized to energy intake); in 1980 and 1986 48-h recall administered by nutritionists Serum fatty acids	Physician diagnosed: allergic rhinitis, allergic dermatitis, asthma (parental questionnaires in 1980, 1986, 1989) Atopic disease: one or more of the above diseases Confounding factors: age, sex, region, maternal education	Follow-up: children who developed atopic diseases in 1989 had consumed less fish in 1980 compared to those who remained healthy (3.2 vs. 6.6 g/1000 kcal; $p<0.001$) Cross-sectional data in 1980: fish consumption was not associated with atopic disease, atopic dermatitis, allergic rhinitis, or asthma Serum EPA and DHA were lower in children with atopic dermatitis in 1980 (1.11 vs. 1.22; $p=0.01$ and 0.64 vs. 0.69; $p=0.01$ respectively) and 1986 (0.91 vs. 1.02; $p=0.02$ and 0.55 vs. 0.61; $p=0.01$ respectively)

Table 3 (continued)

Reference	Study population and design	Exposure measures and exposure assessment	Outcome measures and confounding factors	Findings
[44]	1166 adolescents aged 13-17 years Cross-sectional The 1st Nutrition and Health Survey in Taiwan	Dietary intake including fish during the past month: Total fish Oily fish Shellfish Other seafood 24-h recall and FFQ; administered to children: quartiles of intake	Physician-diagnosed: allergic rhinitis, asthma; (questionnaire to children) Confounding factors: age, levels of urbanization FFQ variables used in the multivariate model: liver, deep-fried foods, oily fish, butcher's meat	Univariate analysis: Higher intake of oily fish (1st vs 4th quartile of intake) was associated with higher prevalence (1.5% vs 4.9%) of doctor diagnosed asthma (p=0.01) Multivariate analysis: total and oily fish intake were not associated with asthma or allergic rhinitis There was no association between any fish category intake and allergic rhinitis No associations found for shellfish and other seafood and outcome measures
[45]	Children aged 6–15 years: 1673 currently asthmatic and 22109 non-asthmatic Cross-sectional The Tokorozawa Childhood Asthma and Pollinosis Study, Japan	FFQ including fish, completed by parents (Japanese Ministry of Health and Welfare): almost none 1–2 times/month 1–2 times/week ≥3–4 times/week	Current asthma (parental questionnaire of the American Thoracic Society and Division of Lung Diseases adopted by the Japan Environment Agency) Current asthma: doctor-diagnosed asthma with symptoms and treatment during the past 2 years Confounding factors: age, gender, parental history of asthma, vegetable and fruit intake	Higher prevalence of asthma among subjects who ate fish 1–2 times/wk compared to those who ate fish 1–2 times/month (OR 1.117; 95% CI 1.005–1.241, p=0.041). Increasing fish intake was associated with increased risk of current asthma (p-trend 0.0349)
[43]	20,271 children aged 7–11 years Cross-sectional 25 areas in 6 Central and Eastern European Countries (Bulgaria, Czech Republic, Hungary, Poland, Romania, Slovakia)	Dietary intake of fish, fresh fruit and fresh vegetable (parental FFQ; redesigned Adult British Survey FFQ): <1/month ≥1/month	Winter cough, persistent cough, wheeze ever, current wheeze (parental questionnaires, ISAAC) Confounding factors: age, sex, area, pets, indoor moisture, gas oven for heating, additional gas heating, passive smoking, maternal education, paternal occupation, parental allergy, respondent, overcrowding, all tested nutritional factors	Low fish intake (<1/month) compared with higher (≥1/month) was associated with increased risk of persistent cough (OR 1.18; 95% CI 1.04–1.34; p=0.01), wheeze ever (OR 1.14; 95% CI 1.03–1.34; p=0.01), and current wheeze (OR 1.21; 95% CI 1.06–1.39; p=0.01)

Table 3 (continued)

Reference	Study population and design	Exposure measures and exposure assessment	Outcome measures and confounding factors	Findings
[47]	4,104 children aged 6-7 years, followed-up for one year Prospective cohort Italian Studies on Respiratory Disorders in Children and the Environment (SIDRIA), part of the ISAAC	Dietary intake including fish (at 1 year follow-up): Pasta with fish: tuna, mackerel, sardines, salmon, anchovies Oily ('blue') fish: tuna, mackerel, sardines, salmon, anchovies Parental semi-quantitative FFQ: never <1 time/week 1-2 times/Hjek ≥3 times/Hjek	12 month occurrence of: wheeze, shortness of breath with wheeze, allergic rhinitis symptoms (parental completion; ISAAC questions at baseline and questionnaire at 1 year follow-up) Confounding factors: sex, study area, paternal education, household crowding, maternal or paternal smoking, dampness or mold, parental asthma	In the univariate analysis: neither oily fish nor 'pasta with fish' were associated with 12 month occurrence of wheeze, shortness of breath with wheeze or allergic rhinitis
[38]	2,531 infants followed up to age 4 years Prospective cohort Oslo Birth Cohort Study, Norway	Introduction of various kinds of food including fish into diet during the year 1 of life Parental questionnaires at age 1 year (no quantitative information): Yes (and month of introduction) No	Doctor-diagnosed current asthma and allergic rhinitis (parental questionnaire administered at 4 years) Confounding factors: parental atopy, atopic eczema at 0–6 months of age, gender, parity, birth weight, maternal age at delivery, birth order, uterus-related pregnancy complications, keeping pets at home when child was born, episode of lower respiratory tract infections during year 1 of life, maternal education, family income per year, maternal smoking at the end of pregnancy, length of breastfeeding.	The risk of allergic rhinitis was lower in children who had fish during the first year of life compared to children who had fish later in life (OR 0.45; 95% CI 0.28-0.74;) Among children who were breastfed for >6 months, those who had fish during year 1 of age had lower asthma risk (OR 0.56; 95% CI 0.36–0.87) and allergic rhinitis risk (OR 0.28; 95% CI 0.15–0.52) Among children without parental hay fever or asthma, those who had fish during year 1 of age had lower asthma risk (OR 0.50; 95% CI 0.30–0.83) and allergic rhinitis risk (OR 0.47; 95% CI 0.25–0.86) Among children with early life atopic eczema, there was a decreased risk of asthma (OR 0.47; 95% CI 0.23–0.97) and allergic rhinitis (OR 0.32; 95% CI 0.15–0.69) with any fish consumption during year 1 Among children without an episode of lower respiratory tract infection during the first year of life, those who had fish during year 1 of age had lower

Table 3 (continued)

Reference	Study population and design	Exposure measures and exposure assessment	Outcome measures and confounding factors	Findings
				allergic rhinitis risk (OR 0.39; 95% CI 0.24–0.66) compared to those who had none The risk of having doctor-diagnosed atopic eczema with symptoms during the 4th year of age was reduced in children who consumed fish during year 1 of life compared to those who did not (OR 0.66; 95% CI 0.52–0.84)
[48]	2978 children, aged 2 years; follow-up to 3 years old Prospective cohort The Prevention and Incidence of Asthma and Mite Allergy (PIAMA) birth cohort study, Netherlands	Dietary intake including fish during the previous month at age 2 years Parental FFQ: Rarely: <1 time/week Regularly: 1–5 times/week Daily: 6–7 times/week	Doctor-diagnosed ever asthma, doctor-diagnosed recent asthma (last 12 months), recent wheeze (parental questionnaire based on ISAAC); posted at age 3 years Confounding factors: sex, birth weight, presence of older siblings, parental allergy, maternal level of education, breastfeeding for at least 8 weeks, smoking in the home and during pregnancy, region, parental asthma	In the univariate analysis eating fish at least once a week was not associated with ever asthma, recent asthma or recent wheeze
[39]	499 children aged 8 years Cross-sectional Childhood Allergy and Respiratory Health Study Tasmania, Australia	Children's total fish intake at age 8 years (parental report): Yes No	SPT, asthma, hay-fever, wheeze, eczema (ISAAC questionnaire to parents) Confounding factors: sheepskin and plastic mattress use during infancy, sex, number of siblings at 8 years, bottle feeding at 1 month, any maternal smoking during pregnancy	Fish intake was associated with decreased risk of ryegrass-pure sensitisation (OR 0.37; 95% CI 0.15–0.90; p=0.03) Fish intake was associated with decreased risk of asthma linked to ryegrass-pure sensitisation (OR 0.20; 95% CI 0.04–0.90; p= 0.04), and the risk of hay fever linked to ryegrass-pure sensitisation (OR 0.25; 95% CI 0.08–0.78; p= 0.02). Fish consumption was associated with a greater reduction in risk for ryegrass-pure sensitisation in comparison to the risk reduction for HDM-pure sensitisation (OR 0.20; 95% CI 0.05–0.79)

Table 3 (continued)

Reference	Study population and design	Exposure measures and exposure assessment	Outcome measures and confounding factors	Findings
[40]	1014 children aged 5–14 years Cross-sectional All primary schools in Knivsta, Sweden	Dietary intake of specific food categories including fish (parental completion in co-operation with the child) Frequency questionnaire: Never <1 time/week 1 time/week >1 time/week daily Assessment of allergens in the school environment	Doctor-diagnosed asthma, current asthma (last 12 months), wheeze, daytime breathlessness, night-time breathlessness, self-reported atopic sensitisation to cat, dog, pollen, food Questions obtained from the European Community Respiratory Health Survey; parental completion in co-operation with the child Confounding factors: age, gender, and all other dietary factors	For an increase of fish intake by one frequency category there was a decreased risk of doctor-diagnosed asthma (OR 0.54; 95% CI 0.35–0.84; $p<0.01$), current asthma (OR 0.51; 95% CI 0.31–0.84; $p<0.01$), and night-time breathlessness (OR 0.36; 95% CI 0.17–0.78; $p<0.05$)
[41]	3619 infants followed up to age 4 years Prospective cohort Stockholm, Sweden	Infant's consumption frequency and time of introducing fish during the 1st year of life Parental questionnaires (at age 1 year): never 1 time/month 2–3 times/month >1 time/week Regular fish consumption defined as ≥2–3 times/week	Assessed at age 4 years (occurrence during last 1–2 years): asthma, eczema, allergic rhinitis, persistent allergic disease, sensitisation (IgE) Any allergic disease: at least one of asthma, eczema, allergic rhinitis Multiple allergic diseases: more than two Confounding factors: parental allergic disease, maternal age, maternal smoking, breastfeeding	Dose-dependent reduced risk for asthma (p-trend 0.03), eczema, allergic rhinitis and sensitization (p-trend< 0.001) with increased in fish consumption frequency Introducing fish at age 3–8 months reduced risk for asthma (OR 0.73; 95% CI 0.55–0.97), eczema (OR 0.77; 95% CI 0.64–0.92), allergic rhinitis (OR 0.77; 95% CI 0.60–0.97) and sensitisation (OR 0.78; 95% CI 0.64–0.95) compared to introducing fish at or after age 9 months Among children without eczema and/or recurrent wheeze during the 1st year of life: fish consumption≥2 times/month compared to≤ 1 time/month during the first year of life was associated with reduced risk of any allergic disease (OR 0.76; 95% CI 0.61–0.94), eczema (OR 0.78; 95% CI 0.60–1.00), rhinitis (OR 0.60; 95% CI 0.43–0.83), sensitisation (OR 0.76; 95% CI 0.57–1.00), persistent eczema (OR 0.48; 95% CI 0.32–0.68), persistent rhinitis (OR 0.43; 95% CI 0.23–0.79) and multiple allergic disease (OR 0.56; 95% CI 0.35–0.89) at 4 year

Table 3 (continued)

Reference	Study population and design	Exposure measures and exposure assessment	Outcome measures and confounding factors	Findings
				Fish consumption≥2 times/ month compared to ≤1 time/month during the first year of life was associated with reduced risk of sensitization (OR 0.52; 95% CI 0.35–0.76; $p<0.01$) only in children without parental allergy
[42]	460 children aged 6.5 years Cross-sectional Menorca, Spain	Children's diet including fish: Total fish Oily fish Non-oily fish Fried/coated fish Seafood Parental completion of semi-quantitative FFQ (modified Harvard questionnaire)	Current wheeze, atopic wheeze (parental completion of questionnaire) SPT (atopy) Confounding factors: gender, maternal and parental asthma, maternal and paternal atopy, maternal smoking, BMI at 6.5 years, maternal and paternal education and social class, breastfeeding, fish intake during pregnancy, number of siblings	There was inverse association between children's total fish intake≥ 60 g/day and atopy (OR 0.43; 95% CI 0.21–0.90; $p<0.05$) Subgroups of fish were not significantly associated with atopy
[49]	4,921 infants aged 1 year Prospective Cohort 'Infants of Western Sweden' Western Sweden	Food frequency data including fish collected at 6 and 12 months of age (Parental completion): never A few times per year 1-3 times per month 1–3 times per week 3+ times per week Lean fish (cod, haddock) Salmon Flatfish Mackerel or herring	Paternal report of eczema. Parental report of food allergy diagnosed by a physician at 6 and 12 months of age Multivariate analysis was performed for those risk factors that were significant in the univariate analysis: maternal eczema, sibling with eczema, bird in the home, introduction of fish before 9 months of age. Also adjusted for 'atopic reasons' for not having furry pets and for cow's milk allergy	Multivariate analysis: Introducing fish before 9 months of age reduced the risk of developing eczema at 1 year of age (OR 0.76; 95% CI 0.62-0.94; $p=0.009$) No influence of the type of fish (lean/oily) consumed Univariate analysis: usually eating lean fish reduced the risk of eczema at 1 year of age (OR 0.81; 95% CI 0.68-0.97; $p=0.025$)—this was not significant in the multivariate analysis

OR odds ratio, *CI* confidence interval, *PUFA* polyunsaturated fatty acids, *HDM* house dust mite, *FFQ* food frequency questionnaire, *ISAAC* International Study of Asthma and Allergies in Childhood, *SPT* skin prick testing, *DHA* docosahexaenoic acid, *EPA* eicosapentaenoic acid, *Ig* immunoglobulin, *AHR* airway hyper-responsiveness, *vs* versus

et al. [42] did not identify any significant association for any of the subgroups of fish included in their FFQ. Nafstad et al. [38] saw a protective effect of introduction of fish early into diet on allergic rhinitis for the whole study population, but this protective effect remained significant only among children who were breastfed for more than 6 months, without parental hay fever or asthma, with early life atopic eczema, or without an episode of lower respiratory tract infection during the first year of life. Similarly, in the other prospective cohort study of Kull et al. [41], although there was a dose-dependent reduction in risk of atopic outcomes with increased fish consumption

frequency, the protective effect was significant only for children without parental allergy. Additionally and in contrast to the study of Nafstad et al. [38], in the study of Kull et al. [41] the results remained significant only for children without eczema and/or recurrent wheeze during the first year of life. Interestingly, introducing fish early during the first year of life (age 3–8 months) was more beneficial than introducing fish later on (age≥9 months) and this was associated with a lower risk of eczema at 4 years of age [41]. This agrees with the findings of Alm et al. [49] who found that the introduction of fish before 9 months of age had a protective effect on eczema in infants at 1 year, lowering the risk by 24% at this age. The rest of the studies which identified a protective effect of fish conducted their analysis for the study population as a whole.

Two studies were identified that found a negative effect of fish consumption on atopic/allergic outcomes in infants/children [44, 45]. Both studies had a cross-sectional design, measuring exposure and outcome at the same time point. This study design is not strong enough to infer causality. Compared to the studies that identified a positive effect of fish consumption, these studies were conducted in older children. Both studies used a FFQ. The FFQ in the study of Takemura et al. [45] was completed by parents. The study of Huang et al. [44], apart from the FFQ, used a 24-h recall and compared the effect between quartiles of intake rather than consumption frequencies. Also, the study conducted by Huang et al. [44] included oily fish in the questionnaire. As far as the atopic outcome measures are concerned, in the study of Takemura et al. [45] questionnaires about atopy were answered by parents whereas in the study of Huang et al. [44] questionnaires were answered by children. Both studies were focused on clinical outcomes and included a component of doctor diagnosis in their questionnaires. The study of Huang et al. [44] excluded subjects with atopic symptoms who were not doctor-diagnosed. Although some confounders were adjusted for in each study, neither adjusted for socio-economic factors. In the study of Takemura et al. [45], comparing children with current asthma and healthy children there were no differences in fish consumption frequencies. However, the increase in risk (12% for current asthma) was significant when comparing the effect of fish intake 1–2 times/month with that of fish intake 1–2 times/week. Also, the authors showed that the risk of current asthma increased with increasing fish intake (p trend= 0.0349). Although the univariate analysis of Huang et al. [44] showed that higher oily fish intake was associated with higher prevalence of doctor diagnosed asthma, in the multivariate analysis this association was no longer significant. Also, no associations were found for total fish, seafood, and shellfish intake and allergic rhinitis or asthma.

Of the three studies that did not identify any statistically significant associations between fish intake and atopic or allergic outcomes in infants/children, two were prospective cohort studies [47, 48] and one was case–control [46]. All studies were conducted in children older than 1 year of age. Hijazi et al. [46] collected fish intake data at age 12 years, Farchi et al. [47] at age 6–7 years and Wijga et al. [48] at age 2 years. All three studies used a parental/maternal FFQ. The study of Farchi et al. [47] was the only one including oily fish and 'pasta with oily fish' as categories. The other two studies collected information only on consumption frequencies of total fish. Also, frequency categories (often, sometimes, rarely, never) in the study of Hijazi et al. [46] were not clearly defined in the questionnaire. What is more, the two prospective cohort studies [47, 48] did not include monthly fish consumption frequencies in their analysis. In contrast, they only compared weekly consumption frequencies which may not have allowed for significant associations to be identified. As far as the outcome measures are concerned, the two prospective cohort studies [47, 48] assessed atopic outcome based on the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaires completed by parents. The ISAAC questions were also used in the study of Hijazi et al. [46], but were answered by the children themselves. Although the two prospective cohort studies had a large sample size, their follow-up lasted only for 1 year which may not have been long enough to allow for atopy/allergy outcomes to be revealed. The cross-sectional data recorded in 1980 during the case-control study, nested in the follow-up study of Dunder et al. [37], identified a null association between fish consumption and any atopic outcome (in 1980). However, as mentioned above, the retrospective follow-up showed a protective effect of fish. In the same study, the cross-sectional data of 1986 were not presented.

Summary and discussion of the findings of these studies

Overall, the evidence from epidemiological studies investigating the effects of fish intake during infancy and childhood on atopic outcomes in those infants or children is inconsistent. However, the majority of the studies (nine of 14) showed a protective effect of fish intake during infancy or childhood on atopic outcomes in those infants/children. The reduction in atopy/allergy risk amongst these studies ranged between 22% and 80%. This variation could be attributed to the fact that studies differed in study design, control of confounding factors, exposure, and outcome measure assessment. Three studies did not observe any associations, and two studies observed increased risk of atopy with higher fish consumption (12% increase of risk for current asthma [45]), although the study of Huang et al. [44] did not show any significant associations in the multivariate analysis. Therefore, based on the evidence available from epidemiological studies, it cannot be clearly

concluded with absolute certainty whether fish consumption during infancy or childhood can be protective towards atopic disease development in those infants/children, although a number of studies would support that conclusion.

Intervention studies investigating the effect of early fish oil exposure on atopic outcomes in infancy or childhood

In general, randomized controlled trials (RCTs) or experimental/intervention studies are designs that provide the highest level of testing of cause and effect. This section reviews the literature published to present on RCTs of fish oil supplementation in pregnancy, lactation, or infancy/childhood and atopy/allergy outcomes in infants/children of those pregnancies or those infants/children (Tables 4 and 5). The studies were identified through Ovid Medline (1950–2009) and Pubmed (1950–2009) databases by searching with the following keywords: fish oil, fish supplements, fish-oil capsules, EPA, DHA, trial, maternal, pregnancy, lactation, atopy, allergy, asthma, eczema, dermatitis, hay fever, pre-school children, childhood, infancy.

Randomized controlled trials investigating the effects of fish oil supplementation during pregnancy or lactation on immune or atopic outcomes in the offspring of those pregnancies

Table 4 summarizes RCTs of maternal fish oil supplementation during pregnancy and/or lactation and immune or atopic outcomes in the offspring during infancy or childhood; five such studies were identified. One study investigating the effects of fish oil supplementation during pregnancy has generated a number of publications [50–57], of which six [50–52, 55–57] refer to atopy/allergy outcomes in the offspring or immune markers that may modulate these outcomes (Table 4). A second study, also investigating the effects of fish oil supplementation during pregnancy on the immune system of the mother and the offspring, has published two papers [58, 59] of which one [58] is included in Table 4. A third study was conducted on lactating women undergoing fish oil supplementation and investigating immune markers, but not clinical outcomes, in the children [60]. The fourth study, conducted by Olsen et al. [61] investigated the effects of fish oil intake in the last trimester of pregnancy and followed up the children to assess asthma at 16 years of age. The fifth study investigated the effects of fish oil supplementation both during pregnancy and lactation, on infant allergy risk. This trial has published two relevant papers, one reporting the effects of the supplementation on the offspring during the first year of life [62] and the other the effects of the supplementation during pregnancy on the immune system of the mother [63].

Description of the five studies

The study of Dunstan and colleagues [50–57] was conducted in Australia and was a double-blinded RCT starting at week 20 of pregnancy. The study of Krauss-Etschmann et al. [58, 59] was a European multicenter (Germany, Spain, Hungary) two-factorial double-blinded RCT starting at week 22 of gestation. The study of Lauritzen et al. [60] was conducted in Denmark and was a double-blinded parallel group RCT including women from The Danish National Birth Cohort. In this study, the women were supplemented during lactation and their children were followed up to 2.5 years of age. The study of Furuhjelm et al. [62] was conducted in Sweden and was a RCT starting at week 25 of gestation up to 3–4 months of breastfeeding. The study of Olsen et al. [61], conducted in Denmark, was a double-blinded RCT with stratification by maternal fish oil intake at baseline (low/medium/high), conducted from week 30 gestation to delivery, and children were followed up at 16 years of age. Furuhjelm et al. [62] compared fish oil with soybean oil as placebo. Dunstan and colleagues [50–57], Lauritzen et al. [60], and Olsen et al. [61] compared fish oil with olive oil as placebo. However, in the study of Lauritzen et al. [60] there was a third group of women which was a high-fish-intake reference group and these women did not receive any supplement. In the study of Olsen et al. [61], there was also a third group which was a control group and which received no oil capsules. Krauss-Etschmann et al. [58] included four groups: DHA-rich fish oil, 5-methyl-tetra-hydrofolic acid (400 μg/day), both, or placebo. All were provided in a milk-based drink. The placebo was a plain milk-based supplement of minerals and vitamins recommended for pregnancy. For the intervention groups, fish oil and/or 5-methyl-tetra-hydrofolic acid were added into the placebo supplement. The main inclusion criterion for the women who participated in the study by Dunstan and colleagues [50–57] was the presence of atopy: all women had a history of physician-diagnosed allergic rhinitis and/or asthma and a positive SPT to one or more of six common allergens. The subjects' habitual dietary intake did not exceed two fish meals per week as assessed using a semi-quantitative FFQ prior to the study. Subjects in the study of Krauss-Etschmann et al. [58, 59] were healthy pregnant women (including both atopic and non-atopic subjects). Only women who did not use fish oil, folate, and vitamin B12 supplementation after week 16 gestation were included in the study. Mothers that took part in the Danish study [60] were healthy and non-atopic. Estimation of their habitual long-chain *n*−3 PUFA intake was conducted using a semi-

quantitative 300 item FFQ and only women with an intake below the population median (0.4 g/day) were randomized. Women with an intake in the upper quartile (> 0.8 g/day) were used as a reference group. In the study of Olsen et al. [61] the women were healthy at study entry (atopic and non-atopic), but those with fish allergy were excluded. Food intake was assessed at baseline by a simple FFQ that categorized women in low, medium, and high habitual intake of fish. In the study of Furuhjelm et al. [62], both atopic and non-atopic women were included (family history of allergy assessed by interview and doctor diagnosis and IgE positive test) and those with fish or soy allergy were excluded. Only women that planned to breastfeed their offspring were included. At baseline (25 weeks of gestation) 3-day dietary diaries were conducted. In both groups, EPA and DHA intakes were 0.2 g/day and 0.1 g/day, respectively [62]. Although the window of early life that the intervention took place differed between the five studies (pregnancy and/or lactation), the duration of intervention period prenatally was similar for three studies: between week 20 of gestation and delivery [50–57], between week 22 of gestation and delivery [58, 59], and between week 30 of gestation and delivery [61]. For one study, supplementation occurred only postnatally, during the first 4 months of lactation [60] and for the study conducted by Furuhjelm et al. [62] supplementation occurred perinatally, starting in pregnancy (week 25) and finishing in lactation (average 3–4 months of breastfeeding). The supplementation dosages of long-chain *n*−3 PUFAs differed between the studies. Women in the fish oil group in the study of Dunstan and colleagues [50–57] received 3.7 g/day of *n*−3 PUFAs with 56% as DHA and 27.7% as EPA. The control group received 4 g/day of olive oil. In the study of Krauss-Etschmann et al. [58, 59], women in the fish oil groups received 0.5 g/day DHA and 0.15 g/day EPA. Women in the study of Olsen et al. [61] received 2.7 g/day EPA plus DHA, while the placebo group (one of the two control groups) received 4 g/day olive oil. In the trial of Furuhjelm et al. [62], the women assigned to the intervention group consumed 1.6 g/d EPA and 1.1 g/d DHA while the placebo group consumed 4.5 g/day soybean oil containing mainly LA. Mothers in the study of Lauritzen et al. [60] were supplemented with 4.5 g/day of fish oil which provided 1.5 g/day of EPA plus DHA or with 4.5 g/day of olive oil. The supplementation in the studies of Dunstan and colleagues [50–57], Furuhjelm et al. [62], and Olsen et al. [61] was in the form of capsules, in the study of Krauss-Etschmann et al. [58, 59], in the form of powder stirred into a milk-based drink, whereas in the study of Lauritzen et al. [60], the fish oil was incorporated into muesli bars, home-made cookies, and capsules. In the study of Dunstan and colleagues, 85% of the women who started the study completed it. Compliance was monitored by measuring the incorporation of EPA and DHA into the cell membranes of erythrocytes [53]. In the European multicenter study [58], there is no reference to subject compliance rates. However, this trial has published results on EPA and DHA incorporation in the mother and offspring [59]. In this paper, it is mentioned that left over sachets of the supplement were asked to be returned. Also, compliance was assessed in standardized questionnaires at 30 weeks gestation, and at delivery by asking each subject how many days of dosing she had missed. The drop-out rate was 13.18% (270 of the 311 recruited pregnant women completed the study) [59]. In the study conducted by Furuhjelm et al. [62], the overall dropout from gestation week 25 till delivery was 17%, however the dropout was higher in the fish oil group (23%) than in the control group (12%). After birth, 52 infants were followed up in the fish oil group and 65 in the control group. This means that the dropout in the fish oil group was 25% and in the control group 13%, while overall, the attrition rate was 19%. Authors did not comment on compliance, apart from the fact that the research nurses contacted the mothers twice during the last part of pregnancy to remind them of the supplementation/placebo [62]. In the study of Olsen et al. [61], children were followed up and assessed in terms of asthma and other related allergic symptoms at 16 years of life. The follow up rate was extremely high, as 522 were included in analyses 16 years after the intervention. According to the authors compliance was optimized by returning and weighing the empty boxes of capsules at three times, so that the researchers estimated amounts of capsules consumed [61]. Lauritzen et al. [60] stated that the overall self-reported compliance with exclusive breastfeeding in both groups was, on average, 91% (range 67–100%, $n=64$). The follow-up rates at 2.5 years of age in the randomized groups and in the high-fish-intake reference group were 72% and 58%, respectively, but in total, the follow-up rate at 2.5 years of infants' age in comparison to the baseline subjects' recruitment was 48% (101 infants out of 211 pregnant women). However, the follow-up women had significantly better compliance with exclusive breastfeeding in the intervention groups compared to the follow-up women in the reference group (89 versus 85%, $p=0.020$) [60]. In the study of Dunstan and colleagues, so as to minimize potential confounding factors at randomization, the groups were stratified by parity (no previous-term-birth child versus one or more), pre-pregnancy BMI, age, and maternal allergy (allergic rhinitis or asthma). Results were adjusted for gender, parity, and method of delivery. Dunstan et al. [50] reported that background maternal dietary intake of fatty acids assessed by FFQ was not different between the two groups at study entry or at 30 weeks gestation. In the study of Krauss-Etschmann et al. [58], after randomization, the women in different groups did not differ significantly in

Table 4 Summary of studies of maternal fish oil supplementation during pregnancy or lactation and atopic or allergic outcomes in infants/children of those mothers

Reference	Subjects and study design	Intervention	Exposure period	Outcome measures	Findings
[50–52, 55–57]	83 Atopic pregnant women Double-blinded RCT Perth, Australia n=40 FO n=43 Control	FO: 4 capsules/day providing 3.7 g/day n−3 PUFA (56% DHA, 27,7% EPA) Control: 4 g olive oil/day (capsules)	From week 20 of pregnancy until delivery	In cord blood: Plasma cytokine concentrations (IL-4, IL-5, IL-6, IL-10, IL-12, IL-13, TNF-α, IFN-γ)	Maternal FO associated with: Lower cord blood plasma IL-13 (p<0.05)
				APC function (HLA-DR expression and cytokine responses)	
				Mononuclear cell cytokine responses to allergens and mitogen (IL-5, IL-10, IL-13, IFN-γ)	Lower cord blood mononuclear cell cytokine responses (statistically significant only for IL-10 in response to cat allergen; p=0.046)
				Plasma total IgE	
				$CD34^+$ hemopoietic progenitors	A higher percentage of cord blood $CD34^+$ cells (p<0.002)
				$CD34^+$ cell expression of cytokine (IL-5Rα, IL-3Rα) or chemokine receptors (CXCR4, CCR3).	
				Eosinophil/Basophil colony forming units	More IL-5 responsive colony forming units (p<0.003)
				Leukotriene production by stimulated neutrophils	Lower neutrophil LTB_4 production (p=0.031)
				In breast milk (3 days post-partum): Immunomodulatory factors - sCD14, IgA, cytokines (IL-5, IL-6, IL-10, TNF-α and IFN-γ)	
				Clinical outcomes at one year of age: SPT	Lower likelihood of a positive SPT to egg (OR 0.34, 95% CI 0.11–1.02; p=0.055)
				Symptoms of allergic disease (asthma, wheeze, food allergy, atopic dermatitis)	Less severity in those infants with atopic dermatitis (OR 0.09, 95% CI 0.01–0.94; p=0.045)
[58]	311 pregnant women, but this analysis on a subgroup Double-blinded 2-factorial RCT Multicenter: Granada, Spain Munich, Germany Pecs, Hungary	4 groups: 1. FO: 0.15 g EPA+ 0.5 g DHA/day 2. 5-MTHF 3. FO+5-MTHF 4. Control: plain milk based supplement FO and 5-MTHF added to control supplement	From week 22 of pregnancy until delivery	Th1/Th2 related molecules in maternal and umbilical cord blood at delivery: mRNA expression of CCR4, IL-13, IL-4, CRTH2, CXCR3, IFN-γ, IL-1, TGF-β	Maternal FO was associated with: Higher TGF-β mRNA in maternal and cord blood at birth (both p<0.001) Lower IFN-γ and IL-1 mRNA in maternal blood at birth (both p<0.001) Lower IL-4, IL-13 and CCR4 mRNA in umbilical cord blood (all p<0.001) Lower proportions of NK cells and $CCR3^+$ $CD8^+$ T-cells in umbilical cord blood (p<0.001 and p<0.04, respectively)
				Cord blood lymphocyte subsets	

Table 4 (continued)

Reference	Subjects and study design	Intervention	Exposure period	Outcome measures	Findings
	n=45 FO *n*=49 5-MTHF *n*=49 FO+5-MHTF *n*=50 Control				
[62, 63]	145 Pregnant women with allergic family history Double blinded RCT Linkoping, Sweden *n*=70 FO *n*=75 Control 117 offspring followed up: *n*=65 Control *n*=52 FO	2 groups: 1. FO: 1.6 g EPA+ 1.1 g DHA/day 2. Control: soybean oil capsules	From week 25 of pregnancy until end of lactation (3-4 months of breastfeeding)	Production of eicosanoids (PGE_2, LTB_4), cytokines (IFN-γ, IL-5, IL-6, TNF, IL-8, IL-10) and chemokines (CCL2, CCL3) by LPS stimulated maternal whole blood cultures Clinical examinations of infants: Skin prick testing to cow's milk, egg, and wheat at 6 and 12 months of age IgE associated eczema and food allergy at 3, 6, and 12 months of age Plasma specific IgE to egg/milk/wheat at 3 and 12 months age	LPS-induced PGE_2 secretion decreased in 64% of the FO-supplemented mothers and increased in 77% of those in the control group ($p=0.002$). The decreased PGE_2 production was more pronounced among non atopic (80%) than atopic mothers (69%) (not significant). LPS-induced cytokine and chemokine secretion was not affected Maternal FO was associated with: Lower prevalence of food allergy (2% vs. 15% in control group; $p<0.05$) Lower prevalence of IgE-associated eczema (8% vs. 24% in control group; $p<0.05$) Lower prevalence of any positive SPT (15% vs. 32% in control group; $p=0.04$) Lower prevalence of positive SPT to egg at 12 months of age (12% vs. 29% in control group; $p=0.02$) Logistic regression analysis revealed that maternal FO was associated with reduced risk of developing any positive SPT (OR=0.36, 95% CI 0.14–0.95; $p<0.05$), a positive SPT to egg (OR=0.31, 95% CI 0.11–0.89; $p<0.05$), and IgE-associated eczema (OR=0.22, 95% CI 0.06–0.81; $p<0.05$) during the first year of life The risk of developing food allergy was 10 fold lower in the FO group compared to the control group (OR=0.09, 95% CI 0.01-0.74, $p<0.05$)
[61]	533 Pregnant women Double blinded RCT Copenhagen, Denmark	3 groups: 1.FO: 4 g/day: 32% EPA, 23% DHA, provided 2.7 g marine *n*−3 LC PUFA/day 2. Control: olive oil capsules (4 g/day)	From week 30 of pregnancy till delivery	Offspring asthma-related diagnosis at 16 years of age: Allergic asthma, asthma of mixed type, atopic dermatitis or allergic rhinitis - data taken from the National patient registry in Denmark	Maternal FO was associated with: Lower risk of asthma (OR=0.37, 95% CI 0.15–0.92, $p=0.03$) Lower risk of allergic asthma (OR=0.13, 95% CI 0.03–0.60, $p=0.01$)

Table 4 (continued)

Reference	Subjects and study design	Intervention	Exposure period	Outcome measures	Findings
	n=266 FO *n*=136 Control *n*=131 No oil capsules Stratification by maternal baseline fish intake 522 children followed up at 16 years after birth	3. No oil capsules			Lower risk of asthma of all types, atopic dermatitis or allergic rhinitis (OR=0.43, 95% CI 0.19-0.96, *p*=0.04) Lower risk of allergic asthma, atopic dermatitis or allergic rhinitis (OR=0.31, 95% CI 0.11–0.84, *p*=0.02)
[60]	Lactating mothers with fish intake below the population median Double-blinded parallel group RCT Denmark *n*=37 FO *n*=28 Control Lactating women with fish intake in the highest quartile: *n*=26	3 groups: 1. 4.5 g FO/day providing 1.5 g/day of *n*−3 LCPUFA 2. Control: olive oil Supplements incorporated in muesli bars, home-made cookies, or capsules 3. Women with high fish consumption—no supplementation	First 4 months of lactation	Cytokine production in endotoxin-stimulated whole-blood cultures at 2.5 years of age Infant plasma IgE levels at 2.5 years of age Parental report of allergy diagnosis or tendency to allergy	Maternal FO was associated with higher IFN-γ production (*p*=0.034) and with a higher ratio of IFN-γ to IL-10 (p 0.019)

RCT randomized control trial, *OR* odds ratio, *CI* confidence interval, *SD* standard deviation, *FA* fatty acids, *PUFA* polyunsaturated fatty acids, *LC* long-chain, *FO* fish oil, *5-MTHF* 5-methyl-tetra-hydrofolic acid, *SPT* skin prick testing, *DHA* docosahexaenoic acid, *EPA* eicosapentaenoic acid, *ARA* arachidonic acid, *CB* cord blood, *CBMNC* cord blood mononuclear cells, *NK* natural killer cells, *APC* antigen presenting cells, *HLA-DR* human leukocyte antigen-DR, *sCD14* soluble CD14, *Eo/BCFU* eosinophil/basophil colony forming units, *Ig* immunoglobulin, *IFN* interferon, *IL* interleukin, *TNF* tumor necrosis factor, *TGF-β* transforming growth factor β, χ geometric mean, *vs* versus

parity, height, weight at study entry, smoking habits, or social demographic characteristics. Also, data on dietary habits were obtained at study entry [59]. However, data on their dietary intake were not presented nor controlled for. The neonates did not differ significantly in sex, birth weight, length, Apgar score, and parental history of allergy. For the purposes of analysis, only 158 mother–child pairs were available. Their characteristics did not differ from those of the main trial (*n*=311). The analysis of this study was adjusted for study center (reference Hungary) and maternal DHA status at week 20 of gestation (baseline). Confounding factors controlled for were gravity, parity, delivery mode, and maternal smoking at 20 and 30 weeks gestation. Olsen et al. [61] did not control for any factors but randomization was stratified by maternal habitual fish intake (low, medium, and high). Furuhjelm et al. [62] made adjustments in their analysis for allergic symptoms in children for the following factors: LA and AA levels in maternal phospholipids at inclusion, breastfeeding fully until 6 months, number of siblings, exposure, to tobacco smoke, maternal allergic symptoms and eczema in family [62]. Lauritzen et al. [60] did not control for confounding

Table 5 Summary of studies of fish oil supplementation during infancy/childhood and atopic or allergic outcomes in those infants/children

Study	Subjects and study design	Intervention	Exposure period	Outcome measures	Findings
[66, 67] CAPS	616 infants with family history of asthma (at least one parent or sibling with asthma) Single-blinded 2× 2 RT Sydney, Australia (6 Hospitals) 554 Children of 616 completed the study at 18 months	Four groups: 1. HDM reduction, placebo supplement 2. No HDM reduction, placebo supplement 3. HDM reduction, FO supplement 4. No HDM reduction, FO supplement FO group: 500 mg/day tuna oil capsules (37% *n*−3 PUFAs), plus canola margarines and oil	From 6 months old or onset of bottle-feeding till 5 years old Placebo group: 500 mg/day sunola oil capsules (0.3% *n*−3, 7% *n*−6 PUFAs, 82% MUFAs, 9% SFAs, 1.7% minor FAs), plus margarines and oil (40% *n*−6, 20% *n*−9, 1.2% *n*−3) Outcomes at 18 months of age	At 18 months: Total serum IgE Lymphocyte cytokine responses to allergen stimulation SPT Parental questionnaire: wheeze, cough, asthma history, eczema Clinical assessment for eczema	High *n*−3 PUFA exposure tended to lower serum IgE FO was associated with a 9.8% absolute reduction (95% CI 1.5-18.1; $p=0.02$) in the prevalence of any wheeze, and a 7.8% absolute reduction (95% CI 0.5-15.1, $p=0.04$) in prevalence of wheeze for more than 1 week High *n*−3 PUFA exposure was associated with a reduction in wheeze ever (p-trend 0.031), doctor visits for wheeze (p-trend 0.047), bronchodilator use (p-trend<0.001) and nocturnal coughing (p-trend 0.032); after adjusting for breastfeeding and smoking during pregnancy, the highest *n*−3 PUFA exposure was only protective for bronchodilator use (OR 0.46, 95% CI 0.30-0.71; $p<0.0001$)
[68] CAPS (as above)	526 Children of 616 completed the study at 3 years of age	As above	As above Outcomes at 3 years of age	At 3 years: Total serum IgE SPT Parental questionnaire: wheeze, cough, asthma history, eczema Clinical assessment for eczema	FO was associated with a 10.0% reduction in prevalence of cough (95% CI, 3.7-16.4; $p=0.003$) in atopic children
[69, 70] CAPS (as above)	516 Children of 616 completed the study at 5 years of age	As above	As above Outcomes at 5 years of age	At 5 years: Total serum IgE SPT Parental questionnaire: wheeze, cough, asthma history, rhinitis, eczema	

Table 5 (continued)

Study	Subjects and study design	Intervention	Exposure period	Outcome measures	Findings
				Clinical assessment for eczema Spirometric lung function, respiratory system resistance measurements	
[71]	64 Healthy Danish infants Randomized, unmasked 2×2 factorial design Copenhagen, Denmark Cow's milk *n*=13 FO *n*=20 Control Infant Formula *n*=20 FO *n*=11 Control	4 Intervention groups: Cow's milk and FO Cow's milk only Infant formula and FO Infant formula only Mean fish oil consumption 3.4 mL/day (571 mg EPA and 381 mg DHA)	From 9th to 12th month of age	Plasma IgE, CRP and sIL-2R concentrations Production of TNF-α, IFN-γ, and IL-10 in whole-blood cultures Fecal IgA at 10 months of age	FO supplementation increased induced IFN-γ production (p=0.05) and tended to decrease induced IL-10 production (p=0.08)
[72]	39 Asthmatic children aged 8–12 years Double-blinded RCT Sydney, Australia *n*=20 FO *n*=19 Control	Intervention: 4 fish oil capsules (0.18 g EPA, 0.12 g DHA/capsule) providing 1.2 g/day *n*−3 PUFAs Diet: canola oil and canola-oil based margarines and salad dressing Control: 4 capsules (0.45 g safflower oil, 0.45 g palm oil, 0.1 g olive oil/capsule) Diet: sunflower oil and sunflower-oil based margarines and salad dressing	6 months	Circulating eosinophil numbers Production of TNF-a by stimulated blood mononuclear cells Lung function SPT Asthma severity (symptoms, medication)	FO decreased TNF-α production compared to baseline (p=0.026) but the magnitude of change between FO and control groups was not significant (p=0.075)
[73]	29 Asthmatic children aged 4-17 years Double-blinded RCT Japan (Hospital setting)	Intervention: 300 mg fish oil in capsules (84 mg EPA, 36 mg DHA) Control: 300 mg olive oil capsules The number of capsules was adjusted to body weight:	10 months	Asthma scoring (observation by pediatricians or nurses) Lung function (acetylcholine challenge)	FO was associated with: Decreased severity of asthma at months 6, 7, 8, 9 and 10 (p< 0.05) Improved lung function at months 6, 8 and 10 (p<0.03)

Table 5 (continued)

Study	Subjects and study design	Intervention	Exposure period	Outcome measures	Findings
	n=15 FO *n*=14 Control	daily dosages of EPA and DHA in the FO group were 17.0-26.8 and 7.3-11.5 mg/kg body weight, respectively			
[74]	21 Healthy children aged 8-12 years Double-blinded RCT Israel *n*=7 FO *n*=14 Control	Intervention: 300 mg/day *n*−3 PUFA (180 mg EPA, 120 mg DHA)+700 mg canola oil Control: 1 g of canola oil Oils were blended in chocolate spread	3 months	Cytokine production (IL-1β, TNF-α, IL-6, IL-10, IL-1ra) by cultured blood mononuclear cells	FO supplementation associated with higher cytokine production in unstimulated and stimulated cultures

RCT randomized control trial, *CAPS* Childhood Asthma Prevention Study, *OR* odds ratio, *CI* confidence interval, *FA* fatty acids, *PUFA* polyunsaturated fatty acids, *MUFA* monounsaturated fatty acids, *SFA* saturated fatty acids, *FO* fish oil, *SPT* skin prick testing, *HDM* house dust mite, *DHA* docosahexaenoic acid, *EPA* eicosapentaenoic acid, *ARA* arachidonic acid, *sCD14* soluble CD14, *CRP* C-reactive protein, *Ig* immunoglobulin, *IFN* interferon, *IL* interleukin, *TNF* tumor necrosis factor, *AHR* airway hyper-responsiveness, *FVC* forced vital capacity, *FEV1* forced expiratory volume in 1 s, *vs* versus

factors in their analysis. However, they assessed subjects' compliance with exclusive breastfeeding, and they found no differences in characteristics of children (2.5 years) between the groups (sex, parity, birth weight, duration and degree of breastfeeding, age, height, weight, family history of atopy, eczema, wheezing, food allergy, plasma IgE).

Findings of the Australian fish oil supplementation study [50–57]

Maternal fish oil supplementation resulted in higher EPA and DHA status and lower AA status in cord blood erythrocytes [53] and in breast milk [52, 57]. Cord blood plasma and urinary F2-isoprostane concentrations, considered to be markers of lipid peroxidation, were lower in the fish oil group [54], suggesting that maternal fish oil supplementation during pregnancy might be protective against oxidative stress in the infants of atopic mothers soon after birth. A number of immunologic effects of maternal fish oil supplementation during pregnancy were reported. These include significantly lower cord plasma IL-13 concentrations [51], a tendency towards lower cord blood mononuclear cell cytokine responses to allergens which was significant for IL-10 in response to cat allergen [50], and lower LTB_4 production and higher LTB_5 production by cord blood neutrophils [56]. Cord plasma IL-13 and cord neutrophil LTB_4 production were inversely related to *n*−3 PUFA status. Although breast milk IgA, soluble CD14 and cytokines were not different between fish oil and control groups, IgA concentration was positively correlated with breast milk DHA [52]. Denburg et al. [55] showed an altered cord blood hemopoietic progenitor phenotype in the fish oil group: there was an increased number of cord blood $CD34^+$ progenitors and an increased number of IL-5 responsive cord blood eosinophil/basophil colony forming units. The number of $CD34^+$ cells in cord blood significantly increased the risk of atopic eczema in infants at 1 year of age, and cord blood progenitor IL-5 responsiveness increased the risk of atopic eczema and recurrent wheeze significantly. Paradoxically, these findings suggest that fish oil supplementation during pregnancy may actually favor the development of atopic disease in the offspring. In contrast to this conclusion, infants in the fish oil group were significantly less likely (OR 0.09) to have severe atopic dermatitis at 1 year of age and were three times less likely to have a positive SPT to egg at 1 year of age (OR 0.34) [50].

Findings of the European multicenter pregnancy supplementation study [58]

Fish oil supplementation with or without 5-methyl-tetrahydrofolic acid resulted in an increased proportion of EPA and DHA in maternal plasma at 30 weeks of gestation and at

delivery and of DHA in cord blood plasma compared with placebo [59]. Fish oil supplementation also increased the percentage of DHA in placental phospholipids, although placental AA was not significantly different between the groups [64]. Fish oil supplementation during pregnancy was associated with lower mRNA expression of IL-4, IL-13, and CCR4 and decreased frequencies of natural killer cells and $CCR3^+$ $CD8^+$ T cells in cord blood [58]. Fish oil during pregnancy also resulted in lower mRNA levels of IL-1 and interferon (IFN)-γ in maternal blood at delivery [58]. In contrast, mRNA levels of the regulatory cytokine transforming growth factor-β were higher in both maternal blood at delivery and in cord blood following maternal fish oil supplementation [58]. Thus, it appears that fish oil supplementation during pregnancy downregulates Th1 responses in the mother and Th2 responses in the fetus. These results are in line with the observations made by Dunstan et al. [51] of lower cord blood IL-13 concentrations after maternal fish oil supplementation. In addition, Krauss-Etschmann et al. [58] showed that the decrease in cord blood IL-13 mRNA levels was more pronounced in non-allergic mothers. No clinical assessments of the infants from this study have been reported.

Findings of the Danish follow-up study [61]

Olsen et al. [61] conducted the fish oil supplementation in 1992 and related late pregnancy fish oil supplementation to prolonged gestation. After 16 years, they followed up the offspring of those mothers that participated in the study and assessed the prevalence of asthma, atopic dermatitis or allergic rhinitis in those children, obtaining the information from the Danish patient registry. The odds ratios for asthma (all types) and allergic asthma were both significantly lower (by 63% and 87% respectively) in the fish oil group in comparison to the olive oil group (control). There was a lower prevalence of asthma (all types), atopic dermatitis or allergic rhinitis (by 57%) and of allergic asthma, atopic dermatitis or allergic rhinitis (by 69%) in the fish oil group compared to control group. Stratification by maternal fish intake at baseline (low/medium/high) did not have any significant effect on the results.

Findings of the Swedish pregnancy and lactation study [62, 63]

Warstedt et al. [63] showed that plasma phospholipid EPA and DHA increased in the fish-oil-treated women during pregnancy with similar changes seen in both atopic and non-atopic women. Lipopolysaccharide-induced PGE_2 secretion from whole blood cultures was decreased in the majority of women in the fish oil group [63]. However, the mean decrease in the fish oil group was not significant, in contrast to the PGE_2 production in the control group which increased significantly. The non-significant decrease of PGE_2 secretion in the intervention group was probably due to the observation of higher secretion at baseline from the mothers that were randomized to the fish oil group compared to those allocated in the placebo group. The change in PGE_2 production differed significantly between the two groups and the decrease in PGE_2 secretion in the fish oil group was more pronounced among non-atopic women (but not significant). No differences in secretion of LTB_4, chemokines, and cytokines were observed with fish oil supplementation.

Furuhjelm et al. [62] associated the fish oil supplementation during pregnancy and lactation (week 25 of gestation to 3-4 months lactation) with atopic outcomes in the offspring at 6 months and 1 year of age. The prevalence of any positive SPT and of a positive SPT to egg in the infants at 1 year of age was significantly lower in the fish oil group compared to the placebo group. Eczema in the presence of detectable IgE antibodies or positive SPT towards egg, milk, or wheat and food allergy (reaction to egg or milk) during the first 12 months of life were significantly lower in the fish oil group. In a regression analysis, after controlling for confounding factors, it was found that the risk of developing any positive SPT, a positive SPT to egg, or IgE-associated eczema was three to four times less in the fish oil group compared to the placebo. The risk of developing food allergy was reduced ten times in the fish oil group in comparison to the control. These significant effects were seen in the offspring of non-allergic mothers but not of allergic mothers.

Findings of the 'Danish National Birth Cohort' study [60]

Erythrocyte *n*−3 PUFAs at 4 months were higher in infants whose mothers received fish oil during lactation compared to controls. Differences in the erythrocyte fatty acid composition between the groups were no longer evident at 2.5 years of age. The study was not powered to look at clinical outcomes, such as atopic sensitization, and no differences in atopic outcomes or in plasma IgE were observed between the groups. No significant association was found between in vitro cytokine production and plasma IgE levels and there was also no significant association between plasma IgE and eczema, wheezing, or food allergy, although both trends tended to be positive.

Summary and discussion of the main findings of these studies

Dunstan et al. [53] showed that maternal fish oil supplementation resulted in higher *n*−3 PUFA status (higher EPA and DHA in cord blood erythrocytes) and lower *n*−6 PUFA status in the neonates. Krauss-Etschmann et al. [59] demonstrated that fish oil supplementation during pregnancy results in higher levels of DHA in both maternal and cord blood. These studies reported effects of maternal fish oil supplementation during pregnancy on cord blood

immune markers (blood cytokine mRNA, plasma cytokines, LTB_4 production from neutrophils, cytokine production by mononuclear cells) and an altered cord blood hemopoietic progenitor phenotype. These immunologic effects might be expected to impact on allergic sensitization and on the development of atopic disease. Indeed, Dunstan et al. [50] reported beneficial effects on atopic outcomes as a result of maternal fish oil supplementation during pregnancy (less-severe atopic dermatitis, lower risk of positive SPT to egg). The Danish study of Olsen et al. [61] identified that fish oil supplementation in late pregnancy is associated with a marked reduction in atopic manifestations in the offspring at age 16 years, suggesting a long-term effect of any immunologic changes that occurred in pregnancy and early life of those children. The study conducted in Sweden [62, 63] involved fish oil supplementation during both pregnancy and lactation. Again, expected effects on *n*−3 PUFA status were observed and these were associated with differences in PGE_2 production. The latter might be expected to influence Th2 polarization. Indeed, infants from mothers in the fish oil group had reduced risk of developing allergic sensitization to egg, IgE-associated eczema and food allergy during the first year of life. The Danish study of maternal fish oil supplementation during lactation [60] is the only one of these studies investigating immune outcomes in the offspring beyond birth. Infants of lactating mothers who received fish oil supplementation had a higher *n*−3 PUFA status at 4 months of age and IFN-γ production at 2.5 years of age was higher in the fish oil group, an observation which may reflect faster maturation of the immune system. This study did not assess clinical outcomes.

Thus, it is clear that fish oil supplementation during pregnancy and lactation results in higher provision of *n*−3 PUFAs to the offspring and so in a higher *n*−3 PUFA status in the offspring. Early fish oil provision is associated with immunologic changes in cord blood and such changes may persist. These studies suggest clinical effects of early fish oil provision including reduced sensitization to common food allergens and reduced prevalence and severity of atopic dermatitis in the first year of life, again with a possible persistence until adolescence with a reduction in eczema, hay fever, and asthma. The observations of these studies need to be confirmed by future trials powered adequately to examine clinical outcomes in the offspring later on in life in order to be able to draw more definite conclusions and to inform recommendations.

Randomized controlled trials investigating the effects of fish oil supplementation during infancy/childhood on allergic outcomes in those infants/children

Table 5 summarizes RCTs of fish oil supplementation during infancy/childhood on allergic outcomes in those infants/children; five studies were identified. Six papers have been published on the Childhood Asthma Prevention Study (CAPS), of which one describes the study protocol [65]. Table 5 summarizes the results of CAPS at 18 months [66, 67], 3 years [68], and 5 years of age [69, 70]. Damsgaard et al. [71] also studied the impact of fish oil supplementation in infants. Studies done by Hodge et al. [72], Nagakura et al. [73] and Vaisman et al. [74] investigated the effect of fish oil in older children.

Description of the five studies

Both the CAPS [65] and the study of Hodge et al. [72] were conducted in Australia, the study of Nagakura et al. [72] in Japan, the study of Vaisman et al. [74] in Israel, and the study of Damsgaard et al. [71] in Denmark. Infants (aged 6 months) who participated in the CAPS [65] were at high risk of developing asthma, whereas infants (aged 9 months) who took part in the Danish study [71] were not selected according to atopy risk. Children (aged 8 to 12 years) who participated in the study of Vaisman et al. [74] were healthy, but those in the studies of Hodge et al. [72] and Nagakura et al. [73] (aged 8 to 12 years and 4 to 17 years, respectively) were asthmatic. All five trials were controlled, comparing fish oil with placebo. The placebos used in the studies varied. The CAPS [65] used capsules containing sunola oil, a monounsaturated fatty acid rich oil which also contains 7% *n*−6 PUFAs. Damsgaard et al. [71] used milk or formula without added oils. Hodge et al. [72] used capsules containing a mixture of palm, olive and safflower oils and also replaced the usual dietary fat sources by sunflower oil and a sunflower oil based margarine. Nagakura et al. [73] used capsules containing olive oil and Vaisman et al. [74] used canola oil blended in chocolate spread. According to these strategies, the five studies provided different sources and amounts of *n*−6 PUFAs to the control group. The mode of provision of fish oil and the dose of long-chain *n*−3 PUFAs given differed among the five studies. In the CAPS tuna oil was given in capsules in an amount that was related to the age of the infant/child: the capsules were added into milk formula if infants had started bottle feeding before 6 months of age, or into formula and weaning foods after 6 months of age. At the highest possible dose infants received 3.6 mg DHA and 0.8 mg EPA per kilogram of body weight [65]. Also canola oil and canola oil-based margarine were used to lower the *n*−6 PUFA intake in the fish oil group, with the aim of achieving a dietary ratio of *n*−6 to *n*−3 fatty acids of 5. In the Danish study [71] liquid fish oil was used providing a mean daily intake of 571 mg EPA plus 381 mg DHA, although the range of intakes was wide, and it was advised to mix the oil into milk or formula. Hodge et al. [72] used fish oil capsules providing 1.2 g EPA+DHA/day and replaced the

usual dietary fat sources with canola oil and canola oil-based margarine. Nagakura et al. [73] used fish oil capsules with the number consumed adjusted according to body weight: thus daily intakes were in the range of 17 to 26.8 mg EPA and 7.3 to 11.5 mg DHA per kg body weight; the heaviest children consumed about 1.4 g EPA plus DHA/day. Finally, Vaisman et al. [74] provided fish oil in chocolate spread delivering 300 mg EPA + DHA/day and in addition provided some canola oil. Three of the studies were double-blinded [72–74], while the CAPS [65] was single-blinded, and the Danish study [71] was not blinded. The CAPS also included a house dust mite exposure modification as a separate arm. The duration of supplementation varied between the studies: 3 months [71, 74], 6 months [72], 10 months [73], and 5 years [65]. Finally, infants and children taking part in these five studies were supplemented during different periods of life. The CAPS conducted the intervention from onset of bottle feeding (or 6 months of age) to 5 years of age [65]. The study of Damsgaard et al. [71] supplemented infants between months 9 and 12 of life. The studies of Hodge et al. [72], Nagakura et al. [73], and Vaisman et al. [74] conducted the intervention on children of a wide age range (8–12, 4–17, and 8–12 years of age, respectively). The differences in duration and dose of fish oil supplementation and in the ages of study subjects among the studies makes direct comparison difficult and may be a source of heterogeneity of findings.

In the CAPS, 68% of the children remaining in the study (excluding those lost to follow-up) were available for assessment and had their blood taken at 18 months of age. At 5 years of age, 84% of the children that participated in the randomized cohort were available for assessment. In the study of Damsgaard et al. [71], the attrition rate was 32% (30 subjects out of 94 dropped out), and the completion rate was 88% (and it did not differ significantly between the groups). In the study of Hodge et al. [72] six children out of 45 dropped out at baseline (13% withdrawal). All children completed the study of Vaisman et al. [74]. In the study of Nagakura et al. [73] one child out of 30 dropped out. In the CAPS, compliance was assessed by counting the number of capsules used. The proportion of parents who reported to have remembered to use the study spreads and oils all or most of the time of the study was 88%, and this proportion was not different between groups [69]. However, when the weight change of the used capsule containers was measured, the median adherence to oil capsules during the period after age 2.5 years was only 56% and was higher in the control versus the fish oil group (62% vs. 51%, $p=0.004$). Damsgaard et al. [71] asked volunteers to return remaining bottles and report any waste: they reported that mean fish oil consumption was 3.4 ml/day (range 0.8 ml to 5 ml/day), which was according to the advice given to the subjects (One to two teaspoonful/day of the oil supplement into milk or formula). Hodge et al. [72] assessed compliance by counting the number of unused capsules by the participants and by food diary records repeated at three time points after dietary modification and supplementation. Mean number of capsules taken per day was three instead of four (for both groups), and there were no children with an average of less than two capsules per day. Moreover, subject compliance was confirmed by the observed changes in plasma EPA levels over the whole period of the trial. Vaisman et al. [74] ensured compliance of the participants by recording the empty containers of chocolate spread in both groups on a weekly basis. However, the compliance rate was not reported. In the study of Nagakura et al. [73], compliance was controlled within a hospital setting.

The CAPS assessed clinical outcomes of atopic diseases in children at three different time points (18 months, 3 years, and 5 years of age). Primary outcomes were asthma and cough at 3 years of age, and probable current asthma at 5 years of age. Wheeze was a secondary outcome measure at 5 years of age. Lung function, atopy, and asthma severity were assessed in the study of Hodge et al. [72]. Asthma severity and lung function were assessed in the study of Nagakura et al. [73]. Blood immune markers, but not clinical outcomes, were determined in the trials conducted by Vaisman et al. [74] and Damsgaard et al. [71]. Blood immune markers were also determined in the CAPS and in the study of Hodge et al. [72].

Findings of the CAPS [66–70]

Fish oil supplementation increased plasma *n*−3 PUFA status and decreased *n*−6 PUFA status at 18 months, 3 years, and 5 years of age. At 18 months of age there was decreased prevalence of wheeze in the fish oil group and higher plasma *n*−3 PUFA levels were associated with lower bronchodilator use, irrespective of the supplementation group [66, 67]. Follow-up at 3 years of age suggested that fish oil supplementation from infancy to childhood could reduce allergic sensitization and airway disease at this early age, as the fish oil group had reduced cough, but not wheeze [68]. However, no effect of fish oil was seen on the other endpoints measured such as eczema, serum IgE concentration, or doctor diagnosis of asthma. At 5 years of age, there was no significant effect of fish oil on any of the clinical outcomes relating to lung function [69], allergy [69], or asthma [70]. Possible reasons for the lack of beneficial effects of long-chain *n*−3 PUFAs at 5 years of age may be related to suboptimal adherence to and/or implementation of the intervention (50% and 56% compliance in the intervention and control group, respectively), as well as to the dose of fish oil used, loss to follow-up and lack of power.

Findings of Damsgaard et al. [71]

Fish oil increased erythrocyte *n*−3 PUFA status. There was a borderline significant effect of fish oil on IFN-γ production by whole blood cultures, which increased, but there were no other significant effects on markers of innate immunity or inflammation, although there was a non-significant trend for reduced IL-10 production.

Findings of Hodge et al. [72]

Fish oil increased plasma phospholipid *n*−3 PUFA status. TNF-α production by isolated mononuclear cells decreased significantly in the fish oil group but was not different from that in the control group at the end of the intervention. There was no effect of fish oil on lung function or asthma severity.

Findings of Nagakura et al. [73]

Fish oil increased plasma EPA status and significantly reduced asthma severity score (by about 70% by month 10) and improved lung function (the provocative concentration of acetylcholine causing a 20% fall in forced expiratory volume in 1 s was increased from an average of 980 μg/ml at baseline to an average of 1,850 μg/ml at month 10).

Findings of Vaisman et al. [74]

All cytokines measured (TNF-α, IL-1β, IL-6, IL-10, IL-1ra) were increased in both unstimulated and lipopolysaccharide-stimulated mononuclear cell cultures following fish oil provision.

Summary and discussion of the main findings of these studies

Provision of long-chain *n*−3 PUFAs in the form of fish oil to infants or children increases the status of those fatty acids in plasma [66, 68–70, 72] and blood cells [71]. Fish oil consumption may induce effects on the immune system in infants [71] and older children [72, 74]. In children with asthma fish, oil did not affect lung function or asthma severity in the study conducted in Australia [72], but significantly improved lung function and asthma severity in the study conducted in Japan [73]. These latter two studies had similar sample sizes. The study of Nagakura et al. [73] used a lower dose of *n*−3 PUFAs than that of Hodge et al. [72], and so this does not explain the differences in outcome observed between these two studies. The study of Nagakura et al. [73] was of longer duration than that of Hodge et al. [72] and did not identify a significant effect of fish oil on asthma score or lung function until month 6 of the intervention; the study of Hodge et al. [72] was of 6 months duration. The studies of Damsgaard et al. [71] in healthy infants and of Vaisman et al. [74] in healthy children did not report clinical outcomes. The CAPS, conducted in infants at risk of allergic disease, is the largest of these studies and involved the longest period of supplementation. This study reported some protective effects of fish oil in these infants at 18 months and 3 years of age [66–68], but these effects did not persist until 5 years at age [69, 70]. Lack of persistence may be due to reduced compliance over time, loss to follow-up, lack of power, or the presence of confounding factors.

Thus, it is clear that fish oil supplementation during infancy or childhood results in higher *n*−3 PUFA status in those infants or children. Such early fish oil provision may be associated with immunologic changes in the blood but it is not clear if these are of clinical significance and whether they persist. Fish oil supplementation in infancy may decrease the risk of developing some manifestations of allergic disease, but this benefit may not persist as other factors come into play. It is not clear whether fish oil can be used to treat children with asthma as the two studies conducted to date [72, 73] give divergent results. Further studies are needed to identify immunologic and clinical effects of fish oil in infants and in children and to identify protective and therapeutic effects and their persistence.

Conclusions

There are two main families of PUFAs, the *n*−6 and the *n*−3 families. Intake of the *n*−6 PUFA LA increased over the second half of the twentieth century, this increase coinciding with increased prevalence of atopy and its clinical manifestations. It has been suggested that there is a causal relationship between *n*−6 PUFA intake and allergic disease and there are biologically plausible mechanisms, involving eicosanoid mediators of the *n*−6 PUFA AA that could explain this. Fish and fish oils are sources of long-chain *n*−3 PUFAs and these fatty acids act to oppose the actions of *n*−6 PUFAs. Thus, it is considered that *n*−3 PUFAs will protect against atopic sensitization and against the clinical manifestations of atopy. Evidence to examine this has been acquired from epidemiologic studies investigating associations between fish intake in pregnancy, lactation, infancy, and childhood and atopic outcomes in infants and children and from intervention studies with fish oil supplements in pregnancy, lactation, infancy, and childhood and atopic outcomes in infants and children All five epidemiological studies investigating the effect of maternal fish intake during pregnancy on atopic or allergic outcomes in infants/children of those pregnancies concluded protective associ-

ations. One study investigating the effects of maternal fish intake during lactation did not observe any significant associations. The evidence from epidemiological studies investigating the effects of fish intake during infancy and childhood on atopic outcomes in those infants or children is inconsistent, although the majority of the studies (nine of 14) showed a protective effect of fish intake during infancy or childhood on atopic outcomes in those infants/children. Fish oil supplementation during pregnancy and lactation or during infancy of childhood results in a higher *n*−3 PUFA status in the infants or children. Fish oil provision to pregnant women is associated with immunologic changes in cord blood and such changes may persist. Studies performed to date indicate that provision of fish oil during pregnancy may reduce sensitization to common food allergens and reduce prevalence and severity of atopic dermatitis in the first year of life, with a possible persistence until adolescence with a reduction in eczema, hay fever, and asthma. Fish oil provision to infants or children may be associated with immunologic changes in the blood but it is not clear whether these are of clinical significance and whether they persist. Fish oil supplementation in infancy may decrease the risk of developing some manifestations of allergic disease, but this benefit may not persist as other factors come into play. It is not clear whether fish oil can be used to treat children with asthma as the two studies conducted to date give divergent results. Further studies of increased long-chain *n*−3 PUFA provision in during pregnancy, lactation, and infancy are needed to more clearly identify the immunologic and clinical effects in infants and children and to identify protective and therapeutic effects and their persistence.

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